# Hawai‘i Journal of Health & Social Welfare

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# Hawai‘i Journal of Health & Social Welfare

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The aim of the Hawai‘i Journal of Health & Social Welfare is to advance knowledge about health and social welfare, with a focus on the diverse peoples and unique environments of Hawai‘i and the Pacific region.

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# Hawai'i Journal Watch

Karen Rowan MS

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

## 'Longevity Gene' Linked with Lower Cardiovascular Disease Mortality in Japanese Men

Japanese men at risk for cardiovascular disease (CVD) who have certain versions of gene called PIK3R1 may have a lower mortality risk over a 30-year period. Researchers including Timothy Donlon, PhD, of the John A. Burns School of Medicine (JABSOM), investigated whether certain PI3K alleles were associated with life span in individuals with and without type 2 diabetes, cancer, and CVD (including hypertension, coronary heart disease, and stroke). The researchers used data on 3568 Japanese men from the Kuakini Honolulu Heart Program/Kuakini Honolulu-Asia Aging Study cohort. At the study's start, the men's ages ranged from 71 to 93, and during the 29-year follow-up period, 3533 of the participants died. Overall, men with CVD had higher mortality than men without CVD. However, the men with CVD who also had a longevity-associated version of PIK3R1 had survival curves similar to men without CVD. Men without CVD showed no association between the longevity-associated genotype and life span, nor was there an association between the gene and life span for men with diabetes or cancer. More research is needed to determine the mechanisms of the association, and the implications for the heritability of healthy aging.

- Donlon TA, Chen R, Masaki KH, et al. Association of growth hormone receptor gene variant with longevity in men is due to amelioration of increased mortality risk from hypertension. *Aging*. 2021;13:10.18632/aging.203133. doi:10.18632/aging.203133

## Antibiotic Hybrids Show Promise in Combating Antibiotic Resistance

Macrocycles are 12- or more membered cyclic molecules that can be synthesized or isolated from natural sources. Recent research suggests that one promising approach to the growing problem of antibiotic resistance is to combine macrocycles with antibiotics into metabolically stable hybrid molecules. In a review article, researchers including Dianqing Sun, PhD, of the Daniel K. Inouye College of Pharmacy, investigated clinical trials of new macrocycle-antibiotic hybrids. Results showed that 2 such compounds are hybrids of vancomycin: TD-1792 has shown activity against MRSA, and TD-1607 has demonstrated a bactericidal effect against Gram-positive organisms. Two other compounds are hybrids of rifamycins. TNP-2092, which is a rifamycin nucleus hybridized with a quinazolinone, shows activity against several types of *Staphylococci* and *Streptococci* bacteria. TNP-2198, a conjugate of rifamycin and another antibiotic called metronidazole, may be effective against bacteria that cause certain vaginal infections. Finally, DSTA3647S, a hybrid of rifamycin and an artificially engineered antibody, may be effective against *Staphylococci* infections. More studies are needed to determine whether these macrocycle-antibiotic hybrid clinical candidates will be developed as new and potential treatment options in the clinic.

- Surur AS, Sun D. Macrocycle-antibiotic hybrids: A path to clinical candidates. *Front Chem*. 2021;9:659845. doi:10.3389/fchem.2021.659845

## Metabolic Syndrome in Native Hawaiians

The prevalence of metabolic syndrome in a population can be difficult to determine because there are varying criteria for diagnosing the condition. The criteria include having high cholesterol, high blood pressure, diabetes or raised glucose levels, and a large waistline. But, for example, the World Health Organization uses a blood pressure of 140/90 mmHg or greater, while the International Diabetes Federation guidelines use a blood pressure of 130/85 mmHg or greater. Researchers including Chloe Asato, a recent bachelor's degree graduate from the Office of Public Health Studies and a current student at JABSOM, examined data from the Native Hawaiian/Multiethnic Health Research project on 1452 Filipino, Native Hawaiian, Japanese, and white residents of Kohala. Results showed the prevalence of metabolic syndrome in the entire study population could be as low as 22% or as high as 39% depending on the definition used. Among Native Hawaiians, the prevalence could be as low as 26.9% or as high as 48.6%. Among all groups in the study, only Native Hawaiians had a significant difference in prevalence depending on which definition was used. The researchers concluded that varying definitions may exacerbate ethnic disparities. More research is needed to identify the best way to define metabolic syndrome.

- Asato CBH, Nelson-Hurwitz DC, Lee T, Grandinetti A. comparative analysis of metabolic syndrome diagnostic criteria and its effects on prevalence in a multiethnic population. *Metab Syndr Relat Disord*. 2021;10.1089/met.2020.0090. doi:10.1089/met.2020.0090

## Opportunistic Measurements of Visceral Fat May Improve Assessments of Women's Cardiometabolic Risk

Obesity is generally assessed using body mass index (BMI), which is simple to determine. However, it is thought that intra-abdominal visceral fat (VAT) may be responsible for many obesity-associated health risks. Researchers including John Shepard, PhD, of the UH Cancer Center, investigated whether VAT measurements obtained from abdominal MRIs were assosciated with having metabolic syndrome. The data came from 1860 older adult members of the Multiethnic Cohort (MEC) study, which enrolled individuals of 5 major racial/ethnic groups including African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites. The researchers calculated participants' VAT measurements from MRI image slices taken at 4 different levels across the abdomen. Results showed that for women, total VAT area as well as the VAT measurements from each of the 4 locations had stronger associations with metabolic syndrome than either BMI or total body fat. Among men, Native Hawaiians showed a stronger association between metabolic syndrome and total VAT area than either BMI or total body fat. The researchers concluded that opportunistic screening for elevated VAT area in women may be warranted across multiple ethnic groups.

- Villegas-Valle RC, Lim U, Maskarinec G, et al. Metabolic syndrome screening using visceral adipose tissue (VAT) from opportunistic MRI locations in a multi-ethnic population. *Obes Res Clin Pract*. 2021;S1871-403X(21)00049-1. doi:10.1016/j.orcp.2021.03.007

# Incident Cases of Sexually Transmitted Infections among Users of Pre-Exposure Prophylaxis for HIV Prevention in Honolulu, Hawai'i

Elizabeth M. Kiefer MD, MPH; Kallan S. Ross MD; Abigail C. Santos MD; Maya R. Barney RN, BSN; Timothy J. McCormick MA; Dominic C. Chow MD, PhD, MPH; and Cecilia M. Shikuma MD

## Abstract

*Emtricitabine/tenofovir disoproxil fumarate [FTC-TDF] is a daily oral medication taken by HIV-negative individuals for pre-exposure prophylaxis (PrEP) to prevent human immunodeficiency virus (HIV) infection. A higher incidence of sexually transmitted infections (STIs) among PrEP users has been reported compared to STI incidence before PrEP use. Asymptomatic incident STI rates were investigated among 78 patients presenting for PrEP in Honolulu, Hawai'i, from April 2018 to May 2019. Testing for oropharyngeal gonorrhea, urethral gonorrhea and chlamydia, rectal gonorrhea and chlamydia, and syphilis was performed. Incident STI percentages were calculated at each follow-up visit. Ninety-seven percent of patients were men who have sex with men (MSM). Forty-seven percent of patients had follow-up data 6 months after initiation and 28% after 1 year. Thirty-two percent of patients self-reported an STI before initiating PrEP. More than half reported anonymous partners. There were 35 positive STI tests during the study period, and 25% of patients had one or more positive tests during this time. At initiation, 17% of patients were found to have an STI, followed by 16% at 3 months, 14% at 6 months, 8% at 9 months, and 5% at 12 months. At all visits, chlamydia was the most common STI detected; at 6 months, 18% of all rectal tests were positive for chlamydia. There were inconsistent condom use and high STI rates from screening during PrEP initiation and follow-up, offering an opportunity to identify asymptomatic STIs in this population. This study is the first report in Hawai'i of STI rates among PrEP users.*

## Keywords

*Pre-Exposure Prophylaxis; Sexually transmitted infections; HIV prevention*

## Abbreviations and Acronyms

*AIDS = acquired immunodeficiency syndrome*
*AST = antibiotic susceptibility testing*
*CDC = Centers for Disease Control and Prevention*
*DC = District of Columbia*
*DOH = Department of Health*
*FTC-TDF = Emtricitabine/tenofovir disoproxil fumarate*
*HIV = human immunodeficiency virus*
*MDR-GC = multidrug-resistant gonococci*
*MSM = men who have sex with men*
*NAAT = nucleic acid amplification test*
*PrEP = pre-exposure prophylaxis*
*PROUD = Pre-Exposure Option for Reducing HIV in the UK*
*RPR = rapid plasma reagin*
*STI = sexually transmitted infection*
*SURRG = Strengthening the United States Response to Resistant Gonorrhea*
*XDR-GC = extensively-drug resistant gonococci*

## Introduction

Emtricitabine/tenofovir disoproxil fumarate [FTC-TDF], a daily oral medication taken by HIV-negative individuals as pre-exposure prophylaxis (PrEP) to prevent human immunodeficiency virus (HIV), was approved in 2012 by the Food and Drug Administration.[1,2] The Centers for Disease Control and Prevention (CDC) recommends PrEP for patients with "substantial risk for acquiring HIV infection," including men who have sex with men (MSM), heterosexual men and women, and injection drug users.[1] For MSM, substantial risk includes those with an HIV-positive sexual partner, recent bacterial sexually transmitted infection (STI), a high number of sex partners, inconsistent or no condom use, or commercial sex work.

FTC-TDF is an effective tool for HIV prevention, as shown in randomized control trials, reducing HIV acquisition in MSM by as much as 92% among subjects with a detectable drug level.[3] An open-label extension of this initial study found a 97% relative reduction of HIV incidence when PrEP was taken on demand.[4] Studies have also demonstrated that rapid high coverage roll-out of PrEP among MSM reduced HIV incidence in the cohort prescribed PrEP and statewide in New South Wales, Australia.[5] New HIV infections decreased significantly in New South Wales from 295 in the 12 months before the roll-out to 221 in the 12 months after the roll-out (relative risk reduction, 25.1%; 95% confidence interval [CI], 10.5–37.4), with only 2 new HIV infections in the nearly 3700 study participants.[5]

Despite this efficacy, studies have indicated that PrEP may be correlated with an increased STI incidence. [6-8] In the general US population, the CDC reports an increase in 2018 STI rates compared to 2017, in primary and secondary syphilis (11 per 100 000 people, an increase of 14%), chlamydia (540 per 100 000 people, an increase of 3%), and gonorrhea (179 per 100 000 people, an increase of 5%).[9] MSM are disproportionally affected by STIs, accounting for nearly 54% of new primary and secondary syphilis cases in 2018.[9] Further, gonorrhea diagnoses doubled among MSM over the previous 5 years (from 186 943 to 341 401 cases).[9] A higher incidence of STIs among MSM PrEP users continues to be reported when compared to STI incidence before PrEP use.[6,7] It is unclear if these increases are

due to a rise in STI testing,[10] an increase in partner numbers,[6] or an increase in condomless anal sex acts.[11] To date, only one study, Pre-Exposure Option for Reducing HIV in the UK (PROUD), an open-label randomized clinical trial comparing immediate to deferred daily Truvada for HIV-negative gay men, was explicitly designed to detect changes in sexual risk behavior by comparing MSM in the United Kingdom who knew they were on PrEP (randomized to immediate start) to those who knew they were not on PrEP (randomized to a 1-year delay).[12] Although there were more condomless sex acts among the participants actively taking PrEP compared to those not on PrEP, there was no increase in STIs among the PrEP group.[12,13]

STI monitoring is also an essential component of the fight against antibiotic-resistant gonorrhea.[14,15] Honolulu, Hawai'i is a sentinel site for gonorrhea surveillance for the Strengthening the United States Response to Resistant Gonorrhea (SURRG) program, which began in 2016.[16,17] SURRG encourages surveillance and capacity building for culture-based gonorrhea surveillance and response. Given that undiagnosed STIs can lead to more severe health problems, including infertility, ectopic pregnancy, and increased HIV risk, STI screening among PrEP users continues to be an important component of PrEP visits and HIV prevention.[18]

This paper describes incident STI rates among asymptomatic patients presenting for PrEP visits at an HIV prevention and treatment clinic for patients in Hawai'i.

## Methods

From April 2018 to May 2019, a chart review was performed of all patients presenting to the clinic for PrEP. Clinic results were collected into a secured de-identified database. As per protocol from the University of Hawai'i Office of Research Compliance Human Studies Program Worksheet 301 sections I and II, this study did not meet the federal definition of research, requiring no further application.

This chart review included patients presenting for their initial PrEP visit and those presenting for subsequent follow-up visits. If a patient was on PrEP at another location, the intake process was the same as a patient new to PrEP, and the first visit at this clinic was still counted as an initial PrEP visit. If the patient started PrEP out of state, they were not included in this study.

Some patients presented within the study period for a follow-up PrEP visit only, comprising the initial visit and some subsequent regular 3-month follow-up visits may have occurred before the study period. Relevant STI data was abstracted from those previous visits. Only patients who initiated PrEP within 12 months of the study period were included in the review.

Information about alcohol use, drug use, partner preference, and history of previous STIs was obtained from the initial PrEP visit. "Some" alcohol use was defined at the time of PrEP initiation as drinking alcohol weekly or monthly. Illicit drug use was defined as any type of drug use at the time of PrEP initiation. At this initial visit, patients were asked whether they used condoms with sexual partners in the previous 90 days. If yes, they were then asked to estimate the percentage of partners with whom they used condoms. Age was determined as the age during the earliest visit associated with the study.

Laboratory work was required before PrEP initiation and included HIV antigen and antibody testing, Testing for hepatitis C antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody, syphilis testing with rapid plasma reagin (RPR), and urine-based urethral gonorrhea and chlamydia testing with nucleic acid amplification test (NAAT). HIV, RPR, and urine-based urethral testing were ordered before each follow-up visit. Testing occurred at a private laboratory or the Hawai'i State Department of Health (DOH). At the initial PrEP visit and each subsequent visit, patients were offered oropharyngeal swabbing to test for gonorrhea, a self-collection kit to obtain a rectal swab for gonorrhea and chlamydia testing, and urine-based urethral testing if it was not done before the visit. Screening is not offered for oropharyngeal chlamydia. Swabbing was done on-site in the clinic. Oropharyngeal and rectal swab specimens were sent to the DOH for NAAT, and results were mailed to the clinic. Patients were notified of their results. Patients with positive results were recalled to the clinic for treatment. For patients with a positive gonorrhea result, a culture specimen was first obtained for antibiotic susceptibility testing (AST), followed by treatment.

The presence of an STI was based on documented laboratory results showing positive oropharyngeal or rectal gonorrhea, positive urine NAAT results for urethral gonorrhea or chlamydia, positive rectal NAAT results for chlamydia, or reactive RPR. All reactive RPRs were confirmed with a treponemal-specific antibody test. Incident STI percentages were calculated based on a denominator of the number of patients tested for that specific STI at each relevant visit.

Screening was also done in the case of patients presenting with an STI contact or symptoms. Gonococcal cultures for AST were obtained before treatment. Treatment was given empirically to symptomatic patients and contacts. However, STIs diagnosed from symptomatic patients and contacts were not included in this study, as this study was investigating the identification of asymptomatic individuals who would otherwise have not undergone treatment. Chart review was done after each visit, and STI testing and results were recorded as they were received.

## Results

From April 2018 to May 2019, a total of 87 individuals on or seeking PrEP presented for a clinic visit. One patient presenting for PrEP was on it previously in another state and was not

included in the study. Eight patients presented for follow-up visits but initiated PrEP more than 1 year prior and thus were not included in the study. Of these 78 patients included in the review, a total of 55 patients (71%) initiated PrEP during the study period. Twenty-three patients initiated PrEP within 1 year prior (29%) and were seen for a follow-up visit during the study period. Patient demographics are summarized in Table 1. The median age was 33 years. The majority of the patients were male (96%), and of those, 93% had only male partners. There were no self-identified transgender patients. Sixty-two percent of patients reported having anonymous partners (4 patients did not report any answer). Thirty-two percent of patients reported having a history of any STI before PrEP initiation. Seventy-six percent of patients reported they used condoms in the 90 days before PrEP initiation (2 of 78 patients did not report condom use status). Among 58 condom users, 36 patients reported an actual percentage of time that they used condoms in the 90 days prior, which was on average 65% (not shown in table). Eighty-two percent reported some alcohol use. Forty-seven percent reported illicit drug use. The most common drug used was marijuana at 33%, followed by "poppers" (amyl nitrite), at 12%.

Table 1. Demographics and Behavioral Variables of Patients at Pre-Exposure Prophylaxis Initiation (N=78)

| | |
|---|---|
| **Demographic** | |
| Initiated PrEP during the study period*, n (%) | 55 (71) |
| Initiated PrEP 1 year before study period*, n (%) | 23 (29) |
| Median age, years | 33 |
| Sex, n (%) | |
| Men | 75 (96) |
| Women | 3 (4) |
| Among 75 men, sex partners, n (%) | |
| Men only | 70 (93) |
| Men and Women | 4 (6) |
| Transgender | 1 (1) |
| Among 3 women, sex partners, n (%) | |
| Men only | 3 (100) |
| Anonymous partners, n (%) | 46 (62) |
| Missing | 4 |
| STI reported before PrEP, n (%) | 25 (32) |
| Reported condom use before PrEP initiation, n (%) | 58 (76) |
| Missing | 2 |
| Weekly or monthly alcohol use, n (%) | 64 (82) |
| Drug use, n (%)† | 37 (47) |
| Marijuana | 26 (33) |
| Poppers | 9 (12) |
| Ecstasy | 5 (6) |
| Other | 4 (5) |

Abbreviation: PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.
*Study period during April 1, 2018, and May 31, 2019
†Some patients reported multiple drug use

Figure 1 illustrates the number and percentage of gonorrhea infections among those tested by the site for each visit. Figure 2 shows the number and percentage of chlamydia infections and the number of new syphilis infections among those tested by the site for each visit. For each figure, the number of cases and the total number of tested patients are also shown by the site for each visit.

At the initial PrEP visit, 78 patients were tested for STIs, and a total of 14 positive tests were detected (Figures 1 and 2). The number of patients tested for specific STIs differed, given that some patients declined specific tests based on their perceived risk, other tests were not ordered, and some patients were tested for certain STIs elsewhere. At the initial PrEP visit, there were 40 completed rectal swabs, 43 oropharyngeal swabs, 65 urine-based tests, and 63 syphilis tests. Seventeen percent of all patients (n=13) presenting for PrEP screened positive for an STI at PrEP initiation. The most common STI detected at PrEP initiation was rectal chlamydia (13% of all patients tested with a rectal swab). Nine percent of all patients tested with an oropharyngeal swab were positive for oropharyngeal gonorrhea. Rectal gonorrhea was detected in 3% of all patients tested with a rectal swab. Urethral chlamydia was detected in 5% of all patients tested, and newly diagnosed syphilis was detected in 2% of all patients tested—one of the 14 patients presented with two positive STI tests.

For the 3-month follow-up visit, 50 patients had STI data. There were 23 completed rectal swabs, 28 oropharyngeal swabs, 36 urine-based tests for urethral gonorrhea and chlamydia, and 24 syphilis tests. A total of 9 positive STI tests were detected (Figures 1 and 2). Sixteen percent of all patients (n=8) at the 3-month follow-up screened positive for an STI. The most common STI detected was rectal chlamydia (13%), followed by oropharyngeal gonorrhea (7%), rectal gonorrhea (4%), syphilis (4%), urethral gonorrhea (3%), and urethral chlamydia (3%). One patient was noted to have two positive STI tests; this individual was previously tested for and treated for two positive STI tests at PrEP initiation.

For the 6-month follow-up visit, 37 patients had STI data. There were 22 completed rectal swabs, 21 oropharyngeal swabs, 25 urine-based tests, and 19 syphilis tests. A total of 9 positive STI tests were detected (Figures 1 and 2). Fourteen percent of all patients (n=5) with 6-month follow-up data had an STI at this visit. One patient presented with 2 positive STI tests, and 1 patient presented with 4 positive STI tests. Two out of the 6 patients had previous positive STI tests detected in the clinic during the study period. The most common STI was rectal chlamydia (18%), followed by oropharyngeal gonorrhea (10%), urethral chlamydia (8%), and rectal gonorrhea (5%). There were no urethral gonorrhea cases and no new syphilis cases.

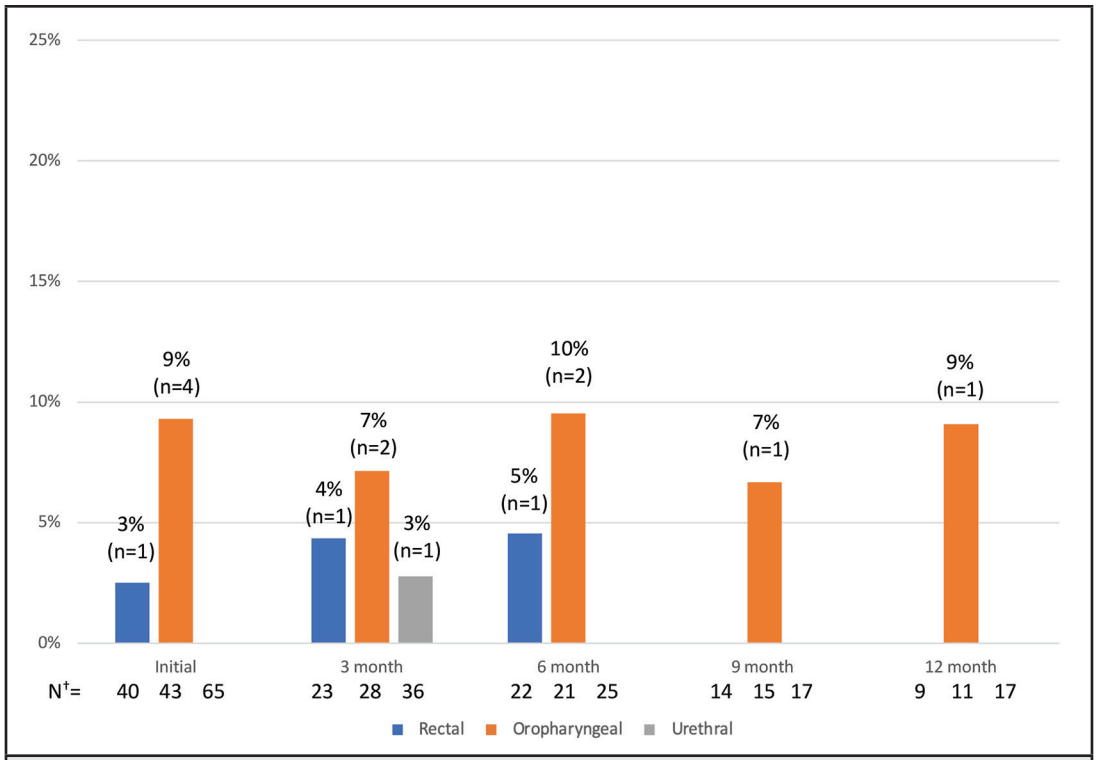


Figure 1. Number and Percentage of Gonorrhea Infections by Site at Initiation and Follow-Up*

*The numbers above each bar are the percentage and number of infections detected.
†N=Total number of patients tested for rectal, oropharyngeal, and urethral gonorrhea, respectively.

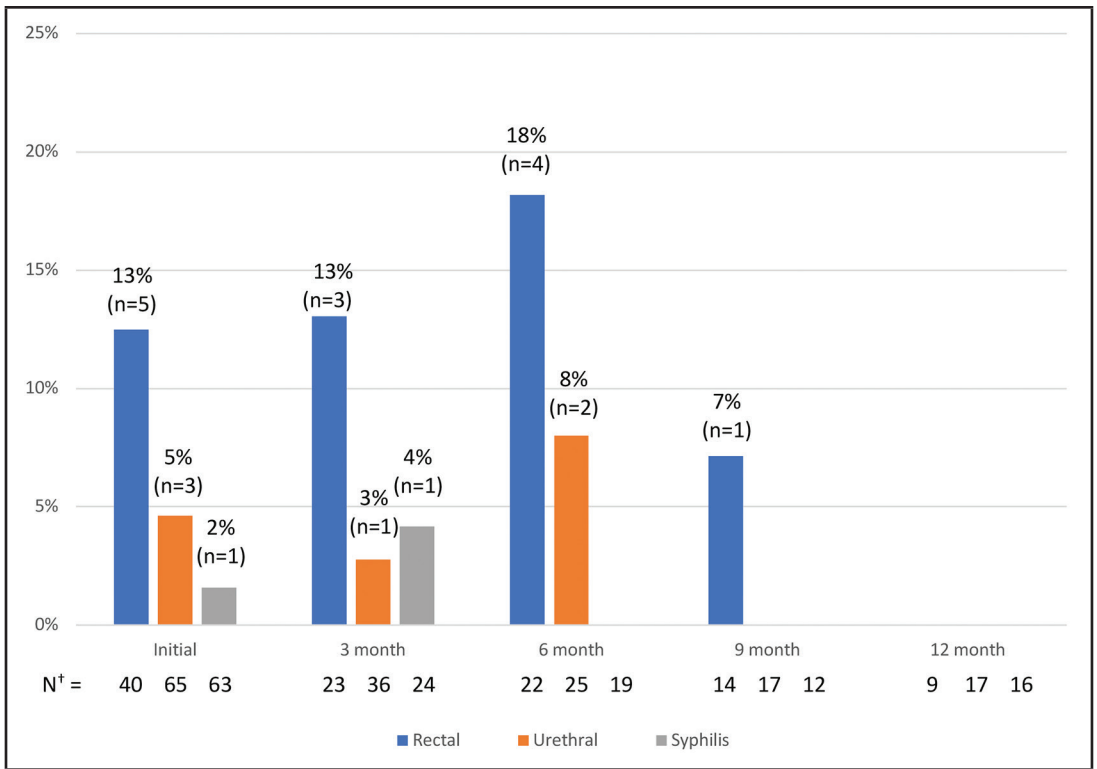


Figure 2. Number and Percentage of Chlamydia Infections by Site and Syphilis Infections at Initiation and Follow-Up*

*The numbers above each bar are the percentage and number of infections detected
†N=Total number of patients tested for rectal chlamydia, urethral chlamydia, and syphilis, respectively.

For the 9-month follow-up visit, 25 patients had STI data. There were 14 completed rectal swabs, 15 oropharyngeal swabs, 17 urine-based tests, and 12 syphilis tests. A total of 2 positive STI tests were detected (Figures 1 and 2). Eight percent of all patients (n=2) with 9-month follow-up data had an STI at this visit. There was 1 positive oropharyngeal gonorrhea test (7%) and 1 positive rectal chlamydia test (7%). Both patients had 1 positive STI test only. Both patients who tested positive at 9 months had previous positive STIs detected in the clinic during the study period.

At 12 months of follow-up, 22 patients had STI data. There were 9 completed rectal swabs, 11 oropharyngeal swabs, 17 urine-based tests, and 16 syphilis tests. One STI was detected (Figures 1 and 2). Five percent of all individuals (n=1) with 12-month follow-up data had an STI at this visit. There was 1 positive oropharyngeal gonorrhea test (9%) (Figures 1 and 2). The patient who tested positive for an STI at 12 months had previous positive STIs detected in the clinic during the study period.

Among the 78 patients during this study period, there were a total of 35 positive test results. Three percent of infections were syphilis (n=2), 13% were oral gonorrhea (n=10), 17% were rectal chlamydia (n=13), 4% were rectal gonorrhea (n=3), 8% were urethral chlamydia (n=6) and 1% urethral gonorrhea (n=1). These 35 positive tests occurred in 20 patients during this study period, representing 26% of the study population. During the study period, 15% percent of patients had 1 positive test (n=12), 5% had 2 positive tests (n=4), 3% had 3 positive tests (n=2), 1% had 4 positive tests (n=1), and 1% had 5 positive tests (n=1).

## Discussion

This study found consistent positive STI tests among asymptomatic MSM on PrEP at initiation and at each of the follow-up visits. To date, this is the first report in Hawai‘i of STI rates among PrEP users. Seventy-eight unique patients were identified who presented to the clinic for PrEP from April 2018 to May 2019, nearly half of whom had follow-up data 6 months after they initiated PrEP. A third of them had follow-up data after 1 year. At all of the visits in this study, asymptomatic STI cases were screened for and detected in this at-risk population. One-third of the study population self-reported an STI before initiating PrEP. This statistic is lower than reports from the PROUD study in England, where 64% of the population reported an STI in the prior 12 months.[12] A quarter of the patients in the present study tested positive for 1 or more STIs, which was also slightly lower than that noted in the literature.[12, 19] A 2016 study by Liu et al of 557 MSM PrEP participants in Miami, DC, and San Francisco found after 48 weeks of follow up, 51% of participants tested positive for 1 or more STIs during quarterly testing (syphilis, rectal gonorrhea or chlamydia, urethral gonorrhea or chlamydia, or oropharyngeal gonorrhea), with 26% of participants testing positive at baseline.[19] The PROUD study detected similar rates as Liu, finding 152 of 265 (57%) participants in the immediate PrEP arm tested positive for 1 or more STIs (243 person-years of follow-up) and 124 of 247 participants (50%) in the delayed PrEP arm tested positive for one or more STIs (222 person-years of follow-up) during routine screening every 3 months.[12] Lower STI rates were demonstrated in Hawai‘i by comparison; however, in the Liu and PROUD studies, each participant was screened regularly as part of the study protocol, while not all of the Hawai‘i participants presenting for 3-month follow-up visits received complete STI testing.

The CDC recommends STI testing every 3 to 6 months; this study demonstrates that testing every 3 months successfully detects asymptomatic infections in this MSM population in Hawai‘i.[1] Seventeen percent of this study population tested positive at PrEP initiation; at most of these follow-up visits, chlamydia was the most common STI. This data is consistent with prior PrEP/STI studies showing high rates of chlamydia among MSM PrEP users, though gonorrhea is also noted in several large studies.[20,21] A study by Traeger et al. in Victoria, Australia found incidences of 45.0 and 39.0 per 100 person-years for chlamydia and gonorrhea, respectively, and similar to this study in Hawai‘i, there was a subgroup of patients who experienced reinfections.[7] This underscores that reinfections are common and that repeat testing every 3 months is effective; at each follow-up visit, positive STI tests were detected among those patients who had positive STI tests at previous visits. At the 9-month and 12-month visit, all positive STI tests were detected in patients with previous positive tests during the study period. The 3-month follow-up interval also provides an opportunity for consistent counseling and education about condom use and risky behavior to prevent further STIs and prevent transmission to their sexual networks and community at the population level.[22] Hsu et al studied characteristics of individuals presenting with repeat STIs within the Massachusetts STI surveillance system; interestingly, data from this state system showed that these patients presented at multiple clinic locations, suggesting that providers might not know the extent of repeat infections and patients' heightened risk.[23] This Honolulu clinic is a large provider of specialized PrEP, HIV, and STI services; therefore, it is in a unique position to provide counseling and STI services to these high-risk patients.

Finally, frequent testing in this MSM population is important for the monitoring of multidrug-resistant gonococci (MDR-GC) and extensively-drug resistant gonococci (XDR-GC) in Hawai‘i. The islands sit geographically near Australia, Japan, Thailand, and China, where resistant strains may reside and be introduced through travel. [24-26]

This study also highlights that patients in Hawai‘i engage in anonymous sexual activity, although this study does not have information about whether this is linked to condom use. While patients in this study reported whether condoms were used in the preceding 90 days before PrEP initiation, data were not

consistently collected about sexual practices before starting PrEP, such as the use of condoms with anonymous partners or the use of condoms per sex act. A major limitation of the study is that it could not determine if anonymous sexual activity or condomless anal sex changed following PrEP. In particular, documentation of condom use included varied responses and did not detail whether condom use decreased after the implementation of PrEP. Further, recall of condom use might be varied or incorrect, especially with multiple partners or multiple sex acts per partner. Prior studies have shown that PrEP may increase risky behavior.[4,12] However, Liu et al showed decreasing condomless receptive anal intercourse in Miami and DC, but not San Francisco,[19] highlighting the need for further study in Hawai'i. The clinic has recently begun to document the number of partners since the last visit. Of these, the number of anonymous partners, the types of sexual acts, and the numbers of partners with whom condoms were used for anal or vaginal sex. This finding represents an area for further research in Hawai'i.

Another major limitation was that not all patients completed multi-site testing for each STI at each follow-up visit due to patient refusal to test for certain STIs or physician error in screening. This limitation could have resulted in missing asymptomatic infections, which would have otherwise been found on routine screening, thus underestimating these results due to missing data. Further, lower STI rates compared to other studies might be due to a smaller Hawai'i population, only one clinic location, and selection bias. Also, the only information regarding STIs before PrEP initiation was based on self-report, and self-reported STIs are notably inaccurate and underestimate the true occurrence.[27] Thus, this study was unable to determine whether there was an increase, decrease, or stable occurrence of STI incidence after PrEP initiation in this population. Additional weaknesses of this study include a small total number of participants and small follow-up numbers. No statistical analyses of associations between patients presenting with STI and possible risk factors were performed. This weakness represents an area for further research.

In conclusion, among 78 patients presenting for PrEP during approximately 1 year, routine screening for STIs produced results consistent with other studies.

## Conflict of Interest

None of the authors identify any conflict of interest.

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# A Comparative Analysis of the Place of Death of Older Adults in Hawai‘i, 2003–2018

Nash A.K. Witten MD

## Abstract

*Studies from around the world have found that the preferred place of death is at home. Although desired, the ability to die at home requires personal, social, and structural factors to be in place. In the United States, between 2003 and 2017, there were decreased hospital and nursing facility deaths and increased home and hospice facility deaths. This study aims to determine whether a change in the place of death in those greater than 65 years of age in Hawai‘i is similar to the overall United States data and if these changes in place of death are similar across islands/counties in the state of Hawai‘i. Data from the Centers for Disease Control and Prevention database were analyzed for natural deaths between 2003 and 2018 in Hawai‘i. Between 2003 and 2018, there were 120 115 natural deaths in Hawai‘i, with a decrease in the overall percentage of deaths in hospitals from 53% in 2003 to 33% in 2018. During the same period, home deaths increased from 23% to 33%, and nursing facility deaths increased from 14% to 16%. This study found that the change in the place of death in those greater than 65 years in Hawai‘i is similar to the overall United States data as a whole, but not within individual Hawai‘i counties.*

## Keywords

*place of death, natural death, home death*

## Introduction

Studies worldwide have found that the preferred place of death for the general population and critically ill patients is at home.[1–6] Patients desire to die at home; however, the ability to die at home requires personal, social, and structural factors to be in place.[7] Personal factors include patient knowledge of the death process, impact and management of end of life symptoms on quality of life, and the maintenance of personal dignity during the dying process.[7] Social factors include the presence of caregivers who can assist and cope with the physical and emotional process of death.[7] Structural factors include reliable medical and social support systems to support both the patient and caregivers and convenient proximity to a hospital for unexpected or uncontrollable symptoms.[7] In 2019, a letter to the *New England Journal of Medicine* analyzed data from the Centers for Disease Control and Prevention for the reported location of natural deaths in the United States between 2003 and 2017.[8] These authors found that there was a decrease in hospital (39.7% to 29.8%) and nursing facility (23.6% to 20.8%) deaths, and an increase in the number of deaths at home (23.8% to 30.7%) and hospice facilities (0.2% to 8.3%).[8] The trends found in the national place of death data support an improving congruence between patient preference[1–6] and health care system utilization.[8] However, the authors found differences in trends between sex, age at the time of death, cause of death, and between racial and ethnic groups.[8]

The Centers for Medicare and Medicaid Services covers the time a clinician spends to perform advanced care planning as part of a Medicare Annual Wellness Visit or under Medicare Part B and tracks the advanced care planning quality metric.[9] The advanced care planning quality metric requires physicians to explain and discuss advanced directives and complete such forms annually with all Medicare patients.[10] In 2016, the Hawai‘i Medical Service Association, the Blue Cross Blue Shield of Hawai‘i, launched a population-based primary care payment model focusing on quality bonuses and a shared savings incentive.[11] Providers that meet or exceed the required percentage of a patient population that completed a monitored quality metric receive a financial incentive from the insurer. This payment model's results were published in 2019, and the advanced care planning quality metric had the highest quality measure improvement under this novel program (40.9% versus 75.7% in the new model group versus 37.0% to 67.2% in the old model group).[11] This increase in advanced care planning quality may be due to increased pressure from the federal and state health insurance industries for quality metric and financial incentive reasons and support patient autonomy. This study aims to determine whether a change in the place of death in those greater than 65 years in Hawai‘i is similar to the overall United States data and if these changes in place of death are similar across islands/counties in the state of Hawai‘i.

## Methods

Data from the Centers for Disease Control and Prevention database for "Underlying Causes of Death, 1998–2018" was summarized and reviewed for natural deaths between 2003 and 2018.[12] Deaths from external causes and outside the state of Hawai‘i were excluded. All data queries included the following criteria: 65–85 years and older, year of death (between 2003 and 2018), and the county in which death occurred. Home deaths included death certificates stating the patient died within the decedent's home. Hospital deaths include medical facility categories of inpatient, outpatient or emergency room, dead on arrival, or unknown. Hospice and nursing home/long-term care home deaths were also queried for this study. All state-level data with less than 10 deaths in any category is suppressed by the Centers for Disease Control and Prevention for patient privacy.[12] Collected data were summarized and reviewed at the state of Hawai‘i and county level using Microsoft Excel, version 16.16.6 (Microsoft Corporation, Redmond, WA).

## Results

Between 2003 and 2018, there were 120 115 natural deaths in Hawai‘i. There was a decrease in the overall percentage of deaths in hospitals from 53% in 2003 to 33% in 2018, as seen in Figure 1. During the same period, home deaths increased from 23% to 33%, and nursing facility deaths increased from 14% to 16%. The percentage of home deaths increased across all counties in Hawai‘i, with Maui County having the most substantial percent increase in the number of home deaths from 24% in 2003 to 42%in 2018, as seen in Figure 2. The percentage of hospital deaths decreased across all counties in Hawai‘i, with the most substantial decrease occurring in Maui County, from 51% of deaths in 2003 to 28% of deaths in 2018, as seen in Figure 3. The percentage of nursing home deaths increased in Kaua‘i County, from 6% in 2003 to 19% in 2018, while the most substantial decrease in the percent of nursing home deaths occurred in Maui County, from 20% in 2003 to 11% in 2018, as seen in Figure 4.

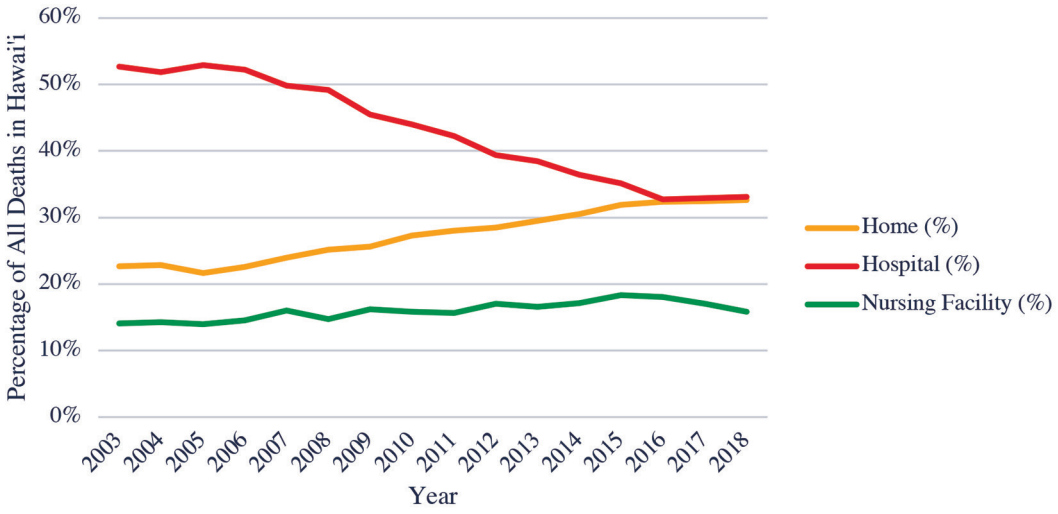


Figure 1. Total Natural Deaths in Hawai‘i Between 1993 and 2018 by Location of Death

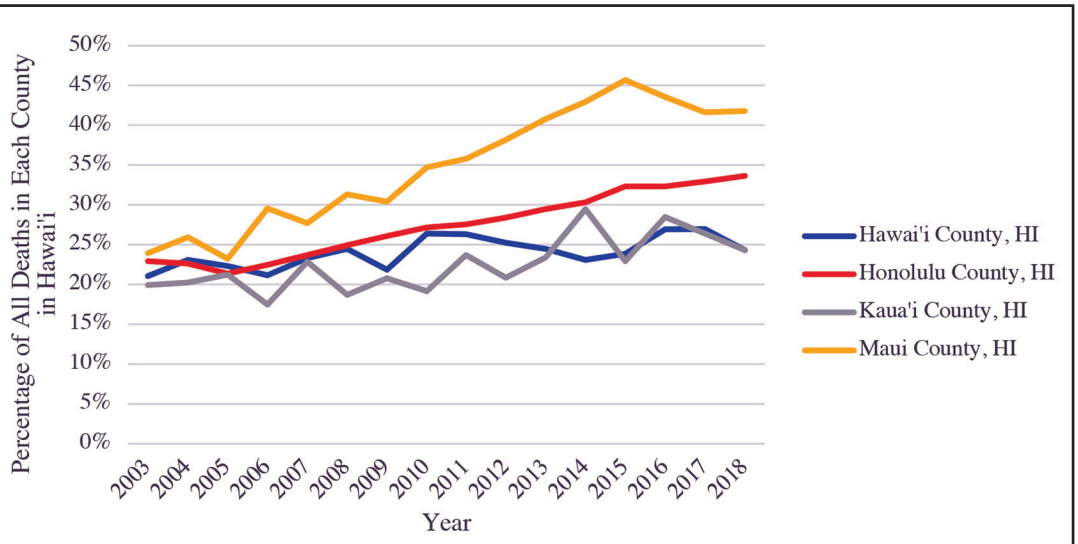


Figure 2. Total Natural Deaths in Hawai‘i Between 1993 and 2018 by Location of Death, At Home, by County

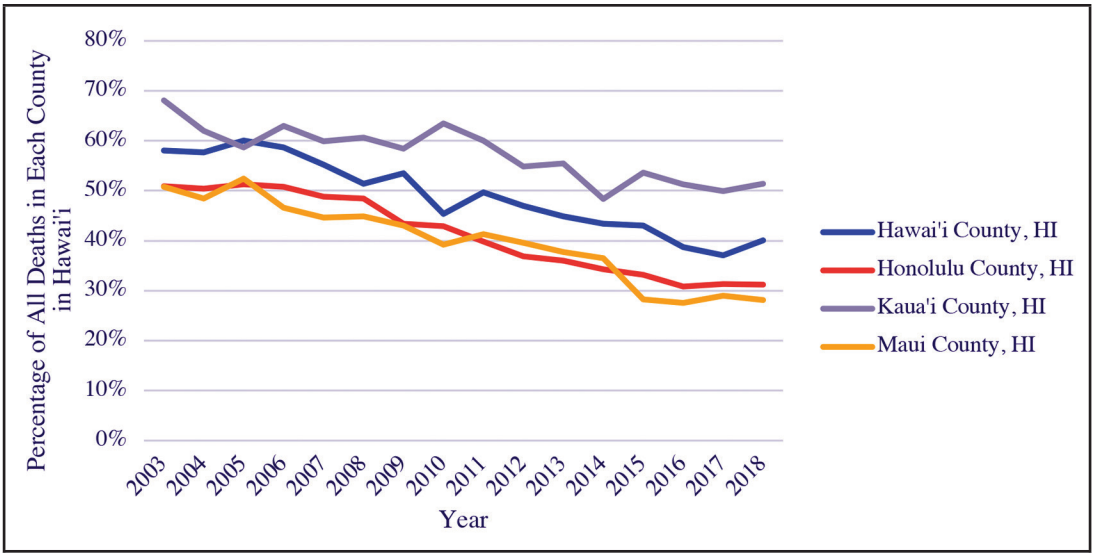


Figure 3. Total Natural Deaths in Hawai'i Between 1993 and 2018 by Location of Death, In Hospital, by County

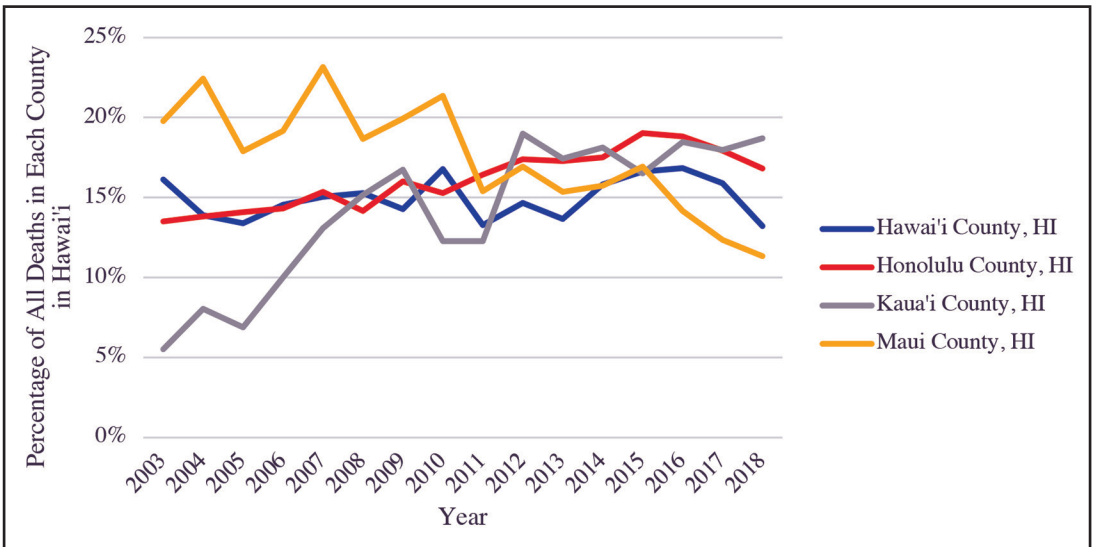


Figure 4. Total Natural Deaths in Hawai'i Between 1993 and 2018 by Location of Death, In Nursing Facilities, by County

## Discussion

The place of death data between 2003 and 2018 in Hawai'i follows a similar trend to the United States between 2003 and 2017, with decreased hospital deaths, increased home deaths, and a relatively stable nursing home death percentage.[8] Numerous studies have shown that the preferred place of death for the general population and critically ill patient is at home, and the United States and Hawai'i health care systems appear to be supporting patient autonomy regarding this decision.[1–6] A 1999 study found ethnic differences related to the preferred place of death in Hawai'i, with 76% versus 43% of white and Chinese, respectively, wishing to die at home.[13] Another study focusing on elder Japanese Americans in Hawai'i found that dying at home was preferred, but dying at a hospital or retirement home were other good alternatives.[14] In contrast, a 2020 study of Marshallese in Hawai'i found that the preferred place of death was in an institution.[15] Although the United States and Hawai'i population, as a whole, may favor home as a place of death,[1-6] specific ethnicity preferences and generational preferences exist, which are important to take into consideration.[15] There is also likely a difference between counties related to the availability of structural factors, such as hospice agency services, that allow individuals to die at home successfully, an area of

needed study. New population-based primary care payment models, such as the Hawai‘i Medical Service Association plan,[11] help promote patient autonomy regarding the place of death, though not necessarily the reason for their implementation. The reimbursement of clinicians for completion of advanced care planning by the Centers for Medicare and Medicaid Services is also likely contributing to patient autonomy regarding the preferred place of death and the change in overall death locations in the United States and Hawai‘i.[10]

Of note, the county of Kaua‘i had an increase in the percentage of deaths occurring at nursing homes than the state of Hawai‘i and United States trends, as seen in Figure 4. The 13% increase in the number of deaths occurring at nursing homes between 2003 and 2018 in Kaua‘i County is surprising as the county has the smallest amount of skilled nursing facility/intermediate care beds in the state (333 beds versus 2588 in Honolulu County, 787 beds in Hawai‘i County, and 459 beds in Maui County).[13] Kaua‘i County also has the smallest number of medicine/surgical beds in the state (68 beds versus 1327 in Honolulu County, 199 beds in Hawai‘i County, and 157 beds in Maui County) and the highest ratio of skilled nursing/intermediate care facility beds in the state (4.9 versus 4.0 in Hawai‘i County, 2.9 in Maui County, and 2.0 in Honolulu County).[13] Further research is needed to determine why Kaua‘i County has more nursing home deaths than other counties in Hawai‘i and the United States.

## Limitations

Kalawao County data, hospice death data, gender death data, ethnicity death data, and “other” location of death data by county was suppressed by the Centers for Disease Control and Prevention due to patient privacy.

## Conclusion

This study found that the change in the place of death in those greater than 65 years in Hawai‘i is similar to the overall United States data as a whole, but not within individual Hawai‘i counties. This trend in Hawai‘i is despite the ethnic and generational differences related to the preferred place of death for people living in Hawai‘i.[13-15] It appears that the financial incentive provided by the Centers for Medicare and Medicaid, as well as new payment models introduced in Hawai‘i, may be contributing to the improved patient autonomy and ability to die at home successfully. It is unclear why Kaua‘i County varies from other Hawai‘i counties and the United States regarding the percentage of nursing home deaths, an area of needed study. Despite the work already being done to improve patients’ ability to die at home, only 33% of Hawai‘i residents were able to die at home compared to 39.7% of patients in the United States. Additional resources are needed to meet the personal, social, and structural factors needed to allow Hawai‘i patients to have the autonomy to die at home, and further insight into ethnic and generational preferences related to the preferred place of death in Hawai‘i is needed.

## Conflict of Interest

I certify that I have no financial affiliation/interest (eg, employment, stock holdings, consultantships, honoraria) in the subject matter, materials, or products mentioned in this manuscript. I have no conflict of interest to report, nor any interests represented with any products discussed or implied.

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# Two-Year Follow-Up of the First Transanal Total Mesorectal Excision (TaTME) Case Performed in Community Hospital in Hawai'i: A Case Report and Literature Review

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## Abstract

*Surgical management of rectal cancer has evolved with the advent of total mesorectal excision (TME) and neo-adjuvant treatment allowing for more sphincter-preserving proctectomies. The laparoscopic approach to TME has numerous advantages over the open approach, including faster recovery, fewer wound complications, and overall reduced morbidity. However, laparoscopic dissection around the distal portion of the rectum is particularly difficult, and thus makes achieving TME completeness and negative resection margins for low rectal tumors a challenge. Transanal TME (TaTME) is designed to overcome these difficulties. It is performed in addition to laparoscopic operation as a bottom-up approach facilitating dissection around the distal rectum. More importantly, TaTME has been shown to have the potential to improve oncological outcomes of minimally-invasive sphincter-preserving proctectomy by providing better TME specimen quality and resection margins. Although interest in TaTME has been growing worldwide, the technique is still relatively new, and adoption into routine practice may be challenging. Potential criteria for successful adoption of the TaTME technique include experience in laparoscopic rectal resection and transanal minimally-invasive surgery (TAMIS), cadaveric TaTME training, and a multidisciplinary approach to selection and management of patients with rectal cancer. Once these criteria are met, gradual and careful implementation of TaTME could be feasible. This report describes the 2-year follow-up of the first TaTME case in Hawai'i managed by a multidisciplinary oncological team in a community hospital setting.*

## Keywords

*Transanal Total Mesorectal Excision, Sphincter Preserving Proctectomy, Hawai'i, Community Hospital*

## Abbreviations and Acronyms

*ACOSOG = American College of Surgeons Oncology Group*
*ALaCaRT = Australian Laparoscopic Cancer of the Rectum Trial*
*CEA = carcinoembryonic antigen*
*COLOR = Colorectal Cancer Laparoscopic or Open Resection*
*CRM = circumferential resection margin*
*DRE = digital rectal exam*
*DRM = distal resection margin*
*ETAP-GRECCAR = Endoscopic Transanal Proctectomy Versus Laparoscopic Proctectomy for Low-Lying Rectal Cancer*
*HMC = Hilo Medical Center*
*IMA = inferior mesenteric artery*
*LaTME = laparoscopic total mesorectal excision*
*MRI = magnetic resonance imaging*
*NCCN = National Comprehensive Cancer Network*
*OpTME = open total mesorectal excision*
*PE = physical exam*
*POD = postoperative day*
*ROLARR = Robotic vs Laparoscopic Resection for Rectal cancer*
*QOL = quality of life*
*TAMIS = transanal minimally invasive surgery*
*TaTME = transanal total mesorectal excision*
*TES = transanal endoscopic surgery*
*TME = total mesorectal excision*

## Introduction

Anal sphincter-preserving proctectomy with total mesorectal excision (TME) remains the mainstream surgical management of patients with stage I to III mid and low rectal cancer.[1,2] Minimally-invasive approaches offer faster recovery, lower morbidity, and comparable oncological results.[3,4] Transanal TME (TaTME) was designed to overcome technical difficulties of transabdominal (laparoscopic or open) dissection around the distal rectum as an additional "bottom-up" approach to TME.[5,6,7] Two highly debated prospective studies, the Australian Laparoscopic Cancer of the Rectum Trial (ALaCART) and the American College of Surgeons Oncology Group (ACOSOG) Z6051 Randomized Clinical Trial, comparing open and laparoscopic sphincter preserving proctectomy techniques failed to demonstrate non-inferiority of laparoscopic approach due to higher number of patients with positive distal resection margin (DRM) in laparoscopic branches.[8,9] TaTME allows for higher certainty in obtaining a negative distal margin due to direct visualization of the rectal mucosa, which remains problematic for a pure laparoscopic approach.[6] Another unique advantage of the TaTME technique is creating reliable circular colorectal anastomosis by avoiding multiple staple load use, which may reduce the risk of anastomotic leak.[10,11] This report is a 2-year follow-up of a case of stage III low rectal adenocarcinoma treated by multidisciplinary oncological approach incorporating the TaTME technique.

## Case Report

A 78-year-old woman presented to a community hospital with rectal bleeding. Her physical exam (PE) was unremarkable, but on digital rectal exam (DRE), she had a palpable partially fixed large polypoid mass at 6 cm from the anus. A colonoscopy showed a large fungating, malignant-appearing mid-rectal mass occupying two-thirds of the rectal lumen. A biopsy revealed a moderately differentiated adenocarcinoma. Staging CT scan showed no distant liver metastases or lymphadenopathy. Carcinoembryonic antigen (CEA) level was 5.2 ng/mL (normal range in adult non-smokers: 0–2.5 ng/mL). An imaging of the pelvis using magnetic resonance imaging (MRI) demonstrated

a T3 tumor invading into perirectal fat and enlarged perirectal lymph nodes. Given these findings, her pretreatment stage was defined as IIIb (T3N1M0).

The case was discussed at a multidisciplinary tumor board meeting with a recommendation of chemoradiation followed by restaging and possible sphincter-preserving proctectomy for the cure. The patient underwent neoadjuvant treatment, including concurrent Capecitabine 650 mg bid for 6 weeks and fractioned pelvic radiation with 25 rounds of 180 centiGray (cGy) x25, and a rectal boost with 3 rounds of 180 cGy, resulting in a total of 5040 cGy.

Restaging demonstrated no metastatic lesions, rectal mass shrinkage, and normalization of CEA level. On exam during her preoperative visit 12 weeks after completion of chemoradiation, she had a small (0.3 cm) residual nodule palpable during a DRE. The area was mobile with the rectal wall.

The patient was elected to be a favorable candidate for TaTME. She underwent laparoscopic mobilization of the left colon and splenic flexure, followed by TaTME using a transanal port with gel cap and pressure maintaining insufflation system. Conventional laparoscopic instruments and a 5-mm laparoscope were used for transanal dissection. Visually adequate distal margin and TME were achieved. In continuation with the previously mobilized sigmoid colon, the dissected rectum was retrieved through the dilated anal canal protected by a plastic wound retractor. This specimen retrieval technique eliminated the need for an abdominal access incision. The specimen was resected at the recto-sigmoid level and removed, completing sphincter preserving proctectomy. An intact mesorectal envelope of the resected specimen was demonstrated on the back table.

A 6-cm sigmoid J-pouch was created outside the anal canal to compensate for rectal volume. The sigmoid pouch was pushed back into the pelvic cavity through the anal canal. A circular stapling colorectal anastomosis was then performed to the remaining rectal cuff under laparoscopic control. The operation was completed by creating a diverting ileostomy using the largest laparoscopic port (12 mm). The two other ports were 5 mm, thereby minimizing transabdominal incisional trauma. Estimated blood loss was 20 mL, and the total operative time was 310 minutes.

The patient was able to ambulate on the same day after the operation and required no opioids for pain control. Her ileostomy started to work normally on postoperative day (POD) 1. She was discharged home on POD 2 without pain medication and on a regular diet. At her 2-week postop follow-up visit, she felt well with a normal appetite and ileostomy function and was able to perform normal daily activities.

Histological examination of the resected rectal specimen demonstrated complete pathological response with no residual tumor detected, intact mesorectal envelope containing 8 lymph nodes, which were all negative for metastatic spread (pT0, N0). The pathologist performed an extensive search to elicit additional lymph nodes in the available mesorectal fat. The radiation effect to the rectum and mesorectal tissue was noted; all margins, including distal and circumferential, were negative. Upon reviewing the surgical and histological findings, the multidisciplinary tumor board's recommendation was not to proceed with adjuvant chemotherapy because of the complete clinical and pathological response and the R0 resection.

The patient underwent uneventful ileostomy reversal 3 weeks after proctectomy. After the ileostomy reversal, she demonstrated bowel function return on POD 2 and was discharged home. She recovered well from this operation, regained weight, and had good bowel function at her 2-week postoperative visit.

The patient was followed up at 3, 6, 12, and 18 months with periodic PE, DRE, and CEA serum levels. At the 2-year follow-up visit, she had a normal PE, DRE (with palpable patent anastomosis), laboratory workup, and CEA level. The patient had no complaints, reported nearly normal bowel function with 2 to 3 bowel movements daily, good anal sphincter control, and a normal quality of life.

## Discussion

### TaTME Versus Laparoscopic and Robotic TME Techniques

Incorporating TaTME into the multidisciplinary treatment of rectal cancer has recently gained popularity due to the potentially unmatched oncological advantages of this technique, specifically for distally located tumors.[12] In TaTME, the rectal mucosa and distal tumor margin are directly visualized, and a purse-string suture is placed to close the lumen beyond the tumor. A full-thickness proctotomy is performed starting at the mucosa layer, tailoring the distal resection margin even for very low tumor locations. Once the distal margin is addressed, the TME is then performed in a caudal to cranial direction, eventually meeting the laparoscopic dissection plane. Not surprisingly, earlier TaTME studies demonstrated zero rates of positive distal margins in resected specimens.[5,6] The anastomosis is then created with a circular stapler when the rectum wall is purse stringed around the anvil, leaving no "ears", corners, or crossed staple lines. This anastomotic technique leaves only a circular staple line, potentially reducing the risk of anastomotic leak.[11] Pure laparoscopic TME may be very difficult, especially in cases with the narrow pelvis or obese male patients. The difficulties of dissection with long straight laparoscopic instruments in the low pelvis are defined by an upward curving of the distal rectum in a narrow space. Even when performed by high-volume laparoscopic colorectal surgeons, these difficulties and the need to use multiple staple loads for rectum transection correspond to a higher number of resections with positive distal margins and subsequent conversion to open procedures.[3,4,8,9] Robotic-

assisted technique offers improved dexterity and accessibility to the distal rectum and may reduce the rate of conversion.[13] However, the robotic approach does not provide any advantage in distal rectum transection as it still requires stapling across the rectum using multiple staple loads, similar to the laparoscopic approach. In a large scale randomized study comparing the results of laparoscopic and robotic rectal resections performed by surgeons with varying experience in both techniques (Robotic vs Laparoscopic Resection for Rectal cancer [ROLARR] trial), no difference in outcomes, including resection margins, was observed.[14]

**Quality of Resected Specimen**

A better specimen quality, consisting of TME completeness and negative margins, might be one of the potential benefits of the TaTME technique.[15,16] Incomplete excision of the mesorectum is a known risk factor for local and overall recurrence.[1,17] Circumferential resection margin (CRM) is an important indicator of TME quality. Involvement of CRM within 2 mm is associated with a local recurrence risk of 16% compared to 5.8% in patients with CRM greater than 2 mm.[18] In a randomized study of 100 patients with low rectal lesions (<6 cm from the anus), positive circumferential resection margins were found to be significantly better when TME was performed via transanal approach as opposed to that of transabdominal (4% versus 10%).[19] A case-matched study comparing TaTME (n=100), laparoscopic TME (LaTME; n=100), and open TME (OpTME; n=100) showed that TaTME resulted in lower rates of incomplete TME specimens than LaTME ($P$=.016). But, when TaTME was compared to OpTME, the difference did not reach statistical significance ($P$=.750).[20] A meta-analysis of 10 studies with 762 patients revealed that TaTME had longer CRM ($P$<.001), a lower positive rate of CRM ($P$<.047), and a longer distal resection margin DRM ($P$<.019) as compared to those of laparoscopic TME.[16] An ongoing prospective study with strict inclusion criteria, standardized technique, and perioperative MRI focusing on CRM may further clarify if there is any advantage of TaTME in regards to better specimen quality and to what degree it corresponds to local recurrence rate and other outcomes.[21]

**Long-term Oncological Outcomes**

The most extensive study to date on long-term oncological outcomes of TME via transanal approach to date was published in 2017 by Marks and colleagues.[22] They followed 373 patients over 5 years, two-thirds of whom were challenging patients such as men with a narrow pelvis, patients with an elevated body mass index, and tumors in the lower third of the rectum. Remarkably, 76% were stage III, and 53% were fixed lesions at presentation. All patients received neoadjuvant treatment and then a diverting ileostomy during surgery. Although the overall local recurrence rate was 7.4%, this was only 4.3% in the laparoscopic abdominal approach group versus 10.8% for the open approach group. Ninety percent 5-year overall survival rate was achieved.

Impressive long-term results have recently been demonstrated in a two-center study from the Netherlands on 159 consecutive mid and low rectal cancer patients. Remarkably, the majority of patients had stage III cancer (T2-3, N1-2), and some (4.4%) had M+ disease (distal metastases) as patients for curative resection of synchronous liver metastasis were included. All patients received neoadjuvant therapy and underwent TaTME with curative intent. The 3-year local recurrence rate was 2%, and the 5-year local recurrence rate was 4%. Disease-free survival was 92% at 3 years and 81% at 5 years.[23]

More data on long-term outcomes of the TaTME approach are underway. The results of Colorectal Cancer Laparoscopic or Open Resection (COLOR) III randomized study designed to assess CRM in laparoscopic TME versus TaTME are awaited. This study will include preoperative and postoperative MRI assessment. Local recurrence rate and long-term oncological outcomes of TaTME will be assessed in relation to margins involvement.[21] A non-inferiority randomized controlled trial called Endoscopic Transanal Proctectomy Versus Laparoscopic Proctectomy for Low-Lying Rectal Cancer (ETAP-GRECCAR) 11 will compare TaTME to laparoscopic TME and include patients with T3 lesions in the lower-third rectum. The main endpoint will be R0/R1 resection with follow-up for 3 years.[24]

**Functional Outcomes**

Up to 60% of patients after rectal cancer surgery report problems with anal sphincter control, sexual and urinary dysfunction, and psychological issues.[25] Damage to pelvic nerves is associated with sexual and urinary dysfunction.[26,27] One of the potential advantages of TaTME over conventional laparoscopic technique is better visualization of the pelvic nerves.[28] Natural drawbacks of the TaTME technique include prolonged anal dilatation and lower anastomosis, which could adversely affect functional outcomes.[29]

In 1 study evaluating functional outcomes of 10 patients undergoing TaTME, pelvic autonomic nerve preservation was intraoperatively assessed with electromyography of the anal sphincter and a cystomanometry using electric stimulations. A variety of functional scores were evaluated preoperatively and postoperatively. Although sexual function and bowel function scores were lower postoperatively, the potential for good function preservation with the TaTME technique was noted.[30]

A study of 30 patients who underwent TaTME and were followed with explicit quality of life (QOL) questionnaires 1 week preoperatively and at 1 and 6 months postoperatively demonstrated that incontinence and dysuria did not change significantly after TaTME. Sexual function deteriorated at 1 month but returned to baseline at 6 months. The authors concluded that functional

outcomes and QOL after TaTME were acceptable and comparable to those of conventional laparoscopic TME.[31]

In a review article by De Nardi, 7 studies addressing QOL and functional outcomes of TaTME were analyzed; most studies reported good outcomes, but each had a small number of patients, and comparative data were lacking.[32] There is a need for larger-scale research. The ongoing COLOR III study is set up to have questionnaires assessing QOL and functional outcomes at 1, 3, 6, 12, 24, and 36 months postoperatively.[21] These results may provide a more meaningful assessment of these important aspects of the TaTME technique.

**Minimizing of Transabdominal Incisional Trauma**

In rectal cancer surgery, a laparoscopic approach is associated with reduced overall complication rates, blood loss, length of hospital stay, and earlier bowel function return.[4] However, specimen retrieval usually requires an additional abdominal incision, which is associated with wound-related complications.[33] In TaTME with a laparoscopic abdominal approach, the specimen could be retrieved transanally or via additional suprapubic incision.[34] The latter method is more suitable for a bulky specimen, long narrow pelvis, or relatively short sigmoid colon.[35,36] In turn, the former approach allows for the elimination of the access incision, leaving only small port incisions and ileostomy.[5] Avoiding incisional trauma including muscle/fascia transection and subsequent suture closure may correspond to earlier patient activation, bowel function return, reduction of wound complication risk and opioid use, as occurred with the patient in this report. However, transanal specimen extraction is not always possible. One should consider this with caution giving priority to oncological safety, good perfusion of sigmoid conduit, and tension-free anastomosis while ensuring adequate left colon length achieved by laparoscopic mobilization.[35,36]

**Areas of Concern**

TaTME is a relatively new technique. Several complications have been reported, including injury of the urethra, urinary bladder, prostate, pelvic nerves, or gas embolism.[30,37,38] As the method has been gradually adopted, there are some reservations about using it widely outside of specialized high-volume centers.[34] Nevertheless, there is increasing interest in learning of TaTME technique worldwide. Several hands-on courses led by world experts are offered and attended by increasing numbers of interested surgeons.[39]

Main intraoperative difficulties may arise from developing incorrect points of dissection as areolar planes created by pneumopelvis may be misleading.[36] If an incorrect plane is entered posteriorly, presacral bleeding may occur, laterally—pelvic sidewall and hypogastric nerve injury, anteriorly—urethra or prostate injury in men.[40] Technical aspects of the bottom-up dissection and correct anatomy and plane recognition could be significantly improved after hands-on training in a cadaveric lab.[39] The importance of a proper training pathway before the incorporation of TaTME into clinical practice has been emphasized.[34,36]

Lessons from the early experience of TaTME in Norway with multifocal local recurrences are now carefully reviewed. Many of them may be related to the procedure's technical aspects, such as open rectal transection and gas flow during TaTME and inadequately tightened purse-string suture that may contribute to spillage of tumor cells.[41,42] Some experts advocate reinforcement of the purse-string closure of the rectum for airtight closure by the placement of a second purse-string suture and washing with a tumoricidal solution to avoid potential tumor spillage and implantation.[43] Essential skills on endoscopic purse-string closure could be developed during cadaveric step-up training.[39,44] Other issues with earlier Norwegian experiences include fragmented experience at multiple facilities and underutilization of neoadjuvant treatment.[41,42,45] Strict adherence to established guidelines on the neoadjuvant treatment of patients with rectal cancer and technical steps of the TaTME procedure may be pivotal.

The learning curve for the TaTME technique could vary and likely depends on individual surgeon experience in laparoscopic colorectal surgery and transanal minimally invasive surgery (TAMIS) or transanal endoscopic surgery (TES).[46,47] The wide range of reported case volume sufficient for proficiency may be explained by the absence of an accurate way to evaluate proficiency in TaTME.[34,35,47] Also, experience from high volume academic centers where cases are bundled among several operators and their trainees cannot be generalized or applicable to community centers where specialized procedures are often concentrated to one set of hands. When TaTME is performed by a single experienced surgeon, operative time can be significantly reduced after the first 4 cases.[48] Individual data on outcomes, such as anastomotic leak rate and functional outcomes, may serve as a proxy for clinical effectiveness in TaTME procedure.[47]

**Feasibility of Performing TaTME at a Community Hospital**

For those surgeons who routinely practice laparoscopic rectal resection for cancer with sphincter preservation in community settings, the TaTME technique may become a valuable part of a surgeon's armamentarium. Bottom-up dissection facilitates excision of the lower third of the rectum. Better visualization of low pelvic structures, distal margin control, and potentially safer anastomosis are particularly appealing.

Could TaTME be safely implemented in a community center with a well-established oncological colorectal care? Unfortunately, due to the lack of randomized data, there are no uniform criteria for safe TaTME practice.[34,35] Some of the expert groups define these criteria as the following: expertise in TME, laparoscopic colorectal surgery, TAMIS, and intersphincteric dissection. Practicing in cadaver models, proctoring the first

cases by experts in the field, and entering data in a registry are advocated.[44,46] The role of the multidisciplinary team in patient selection is emphasized.[36,49]

In the East Hawai'i community, there has been a well-established colorectal oncological service. Relative geographic isolation and coverage of the major portion of the island population provide a steady volume of patients with rectal cancer presenting to Hilo Medical Center (HMC). All cases are managed by a multidisciplinary team, including a radiation oncologist, medical oncologists, radiologists, pathologists, and general surgeons who practice laparoscopic colorectal resection. The patients with potentially resectable lesions and clinical stage II and III undergo neoadjuvant chemoradiation. All low rectal resections and TME are performed by a single established team of 2 surgeons. The operating surgeon is trained in minimally-invasive surgery, has 2 decades of experience in colorectal resections, and underwent training courses on TaTME, including a 3-day hands-on cadaveric course. Pathology evaluation of TME specimens in HMC has been performed based on The National Comprehensive Cancer Network (NCCN) recommended principles of pathological review. Specific attention is paid to TME completeness on gross examination and CRM and DRM distances.

TAMIS was implemented in routine practice in HMC 5 years ago. Multiple cases for benign and T1 rectal lesions have been performed since using GelPOINT access platform (Applied Medical, Rancho Santa Margarita, CA) and Airseal system (CONMED, Utica, NY) for steady insufflation. These 2 platforms are used for TaTME by a majority of experts.[35] In the laparoscopic approach, mobilization of the splenic flexure, high ligation of inferior mesenteric artery (IMA), and diverting ileostomy is routinely performed according to the recommended steps by a majority of expert groups.[35,36,50] An enhanced recovery protocol is implemented in all patients postoperatively, which includes early feeding, ambulation, and limited opioid use.

The patient for the pilot TaTME case was chosen after a careful patient selection process. The potential candidates were discussed at the multidisciplinary tumor board. The specific goal was to assure technical success and acceptable long-term results of the first TaTME case before the broader implementation of this technique in the settings of HMC. In preparation for the case, the operating surgeon completed the last hands-on TaTME course 2 weeks before the scheduled date of operation. An extensive review of video cases, including pitfalls and errors, was performed. Although proctoring by direct intraoperative observation was not feasible due to organizational difficulties, the case and detailed operative plan were discussed with a world expert, who was readily available by phone during the operation. There were no intraoperative issues or significant deviations from the discussed plan. The early results of the first Hawaiian TaTME case performed in 2017 (blood loss, operative time, TME completeness) were remarkably similar to those of the first reported by Lacy's group (2010), and comparable to those of the first case in the United States (2016) as reported by McLemore et al.[5,46] Furthermore, at 2-year follow up this patient remains free of the disease with good functional outcome.

## Conclusion

Adopting the TaTME technique in community hospitals could be feasible if an appropriate training pathway and a multidisciplinary approach are implemented. Although the long-term oncological and functional outcomes of our first TaTME case are encouraging, case series with a higher number of patients and long-term outcome data will be required to demonstrate comparable results to published data. A careful balance between sufficient safety and adequate efficacy of practicing of TaTME technique at a community hospital should be maintained.

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# Pacific Tracker (PacTrac) Version 3.1 Diet and Physical Activity Assessment Tool for the Pacific Region

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## Abstract

*The Pacific Tracker (PacTrac) is a web-based diet and physical activity assessment program created to analyze dietary recall or dietary record data from the Pacific region. Version 3.1 modifications make the tool available for public use (under check it out) to enter, analyze, view and print out data; and for research use, for saving and downloading of multiple entries in a research mode. PacTrac 3.1 (https://nappactrac31.ctahr.hawaii.edu/default.htm) is managed through the Children's Healthy Living Center of Excellence (CHL Center) at the College of Tropical Agriculture and Human Resources at the University of Hawai'i, in collaboration with the University of Hawai'i Cancer Center.*

## Keywords

*Diet, Physical Activity, Nutritional Assessment, Pacific Islander, Children*

## Introduction

Our purpose is to describe the Pacific Tracker version 3.1 (PacTrac 3.1) and its evolutionary history. PacTrac 3.1 is an online diet and physical activity assessment application that can be used to evaluate dietary and physical activity recall or dietary record data for the Pacific region. The discontinuation of the US Department of Agriculture (USDA) Supertracker application on June 30, 2018 has created a void of publicly and professionally available tools to evaluate diet and physical activity for adults and children.[1] The Supertracker web-based application allowed for free 24-hour dietary assessment and tracking. This void is accentuated by the lack of both public and professional resources that contain foods consumed in the Pacific region. The Pacific Tracker (PacTrac), developed at the University of Hawai'i, aims to fulfill this deficit.

The United States (US) federal government has not collected dietary data in Hawai'i since the Nationwide Food Consumption Survey (NFCS) of 1977-78, and never in the broader US-Affiliated Pacific (USAP) Region.[2] The National Health and Nutrition Examination Survey (NHANES), which succeeded NFCS, has not surveyed in Hawai'i nor in the Pacific region jurisdictions with US political affiliations: the state of Alaska bordering the Pacific Ocean; the Pacific island US territories of Guam and American Samoa; the Commonwealth of the Northern Mariana Islands (CNMI); and Palau, Marshall Islands and the Federated States of Micronesia which are Pacific Island nations that are in a compact of free association relationship with the US. This has resulted in no federal record of dietary intakes in the region, and a lack of the Pacific region's foods in the USDA database; if foods are not identified in the NFCS or, at present, in the NHANES, they are not eligible for nutrient analysis in federal laboratories.[3] These same national food databases are also those used for deriving US dietary patterns underpinning US Dietary Guidelines and related food programs and policies. Thus, nutrient-dense regional foods are not recognized or encouraged, which also may promote greater reliance on importation of recognized foods into the region. While the core of the PacTrac tools derive foods and methodologies from the USDA databases, composition data from foods identified in our studies, predominantly on children, have been added from published food composition data from other laboratories that follow national and international guidelines for food composition analysis and database development.[4] For example, South Pacific work on food composition tables for the Oceania region produced a useful database that has been incorporated into the PacTrac.[5]

Only a few studies previously analyzed children's diets in the USAP. The first studies implemented proprietary tools of USDA data from the 48 contiguous states, from which foods substitutions were made to approximate local foods.[6,7] since then versions of the PacTrac have been used in these studies.[7,8]

PacTrac was initially developed from MyPyramid Tracker, the USDA's Center for Nutrition Policy and Promotion, which was an online interactive dietary-assessment tool designed for use by the public.[9] PacTrac was initially established for the Healthy Living

in the Pacific Islands (HLPI), Healthy Pacific Child Program to analyze dietary intakes of children in the CNMI and Hawai'i.[10] PacTrac Version 2 involved adding the first Pacific Island foods, including the University of Hawai'i Cancer Center's Nutrition Shared Support and Biostatistics Shared Resources foods and recipes specific to the diets of the Pacific Islands' populations.[11] This food composition table (FCT) includes a wide range of items, including indigenous Pacific Island and Alaskan foods, as well as the American and Asian foods that are commonly eaten in the region. The database for PacTrac 2 consisted of 2,737 foods from Nutrition Support Shared Resource (NSSR), plus 85 recipes from Guam, 40 recipes from CNMI, and 41 foods from Hawai'i that were consumed by children. PacTrac 2 was initially employed in the Pacific Kids DASH for Health (PacDASH) study where the addition of an "Expert System" provided targeted diet and physical activity guidance and was used in an intervention study that provided clinical guidance.[12] PacTrac 2 is not currently in use.

PacTrac Version 3 was developed for the Children's Healthy Living Program for Remote Underserved Minority Populations of the Pacific (CHL) program data collection and data entry of Food and Activity logs from across the US affiliated Pacific Region, adding more foods and recipes, especially indigenous ones for children.[13] The tool computes daily dietary components upon saving of the dietary record or recall. PacTrac 3 also allowed entry of activities performed while eating, such as watching TV or riding in the car. The dietary portion of PacTrac 3 generates two data tables that were used for data analysis. The input table contains the names of the foods and beverages recorded with 1 data row per food/beverage entered and associated with a user ID, record date, record time, portion size, and other relevant variables. The output table includes derived food component groupings based on the input data. The output file has 1 record per day per user ID, including the date of the record. For the physical activity assessment, children's physical activity metabolic equivalents were added from Ridley, Ainsworth and Olds;[14] 178 children's physical activities were incorporated. Two tables are generated for physical activity. The input table includes times of activity and the intensity group. The output table includes METs (metabolic equivalents of activity) and minutes in each activity level per day per user ID.

The PacTrac 3 was used to enter 210,395 food items on 13,673 food records for the CHL Program. Wrappers, labels and packages of foods were collected during the CHL program and used to aid in entry of the food records.[15] The dietary component analyses created from PacTrac 3 for CHL are being used in study publications.

PacTrac Version 3.1 made the tool available publicly available for individual day analysis as well as for professional use, allowing data analysis and saving of multiple dietary recalls or dietary records. The publicly available online dietary and physical activity assessments provide comparisons to guidelines for diet and physical activity, and provides related nutrition and physical activity messages, and links to nutrient and physical activity information. To provide individuals a better understanding of her/his diet or physical activity over time, data can be tracked for up to a year. Figure 1.

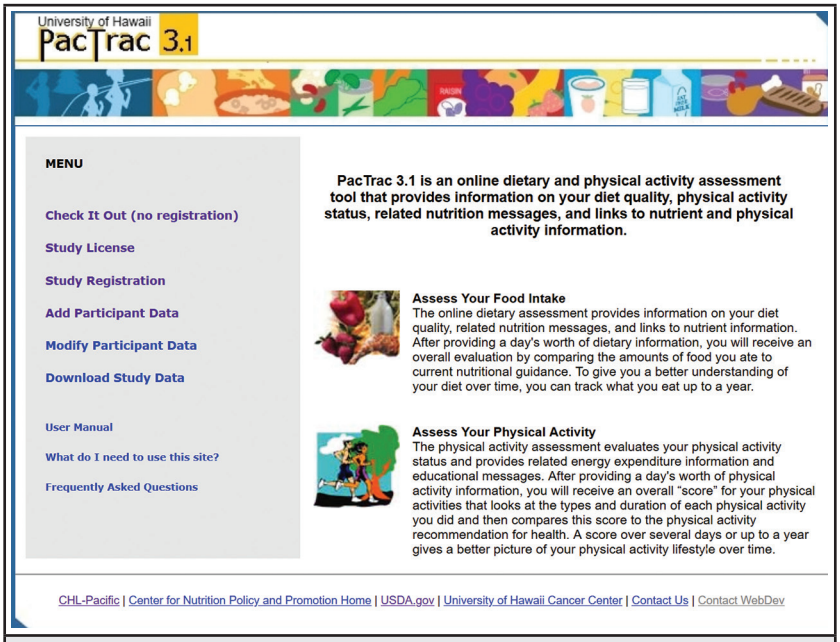

Figure 1. The PacTrac 3.1

Pacific Tracker Version 3.1 (PacTrac 3.1) was modified with the CHL Center of Excellence. The software was upgraded with Microsoft Visual Studio. Net 2012, and related frameworks. The FCT was enhanced to add new 344 Pacific foods from the CHL Program plus alcoholic items, which had not been included in the child only studies.

PacTrac 3.1 was developed to modify PacTrac version 3 for a range of public and professional purposes. The tool has a public use function for entry, analysis, view and printing of data. For professional use, the tool allows registration of a research study, entry and analysis of data and, as a new feature for end users, download of Excel or ASCII data sets. The PacTrac 3.1 program is available on the web[16] and is managed through the CHL Center at the College of Tropical Agriculture and Human Resources at the University of Hawai'i, in collaboration with the University of Hawai'i Cancer Center.

PacTrac 3 and 3.1 are concurrently in use. PacTrac 3 for CHL research and PacTrac 3.1 will continue to be available to the public and professional use for new studies. Dietary output of food components (nutrients and food groups) reflect US Dietary Guidelines and the Healthy Eating Index (HEI) from 2005.[17] While updating of the HEI may be possible with new resources, each five-year update of the HEI has been found equally valid and reliable for assessing diet quality[18] for ages 2 and above. On the other hand, the physical activity output of PacTrac was designed for CHL and targets children's physical activity needs.

## Discussion

The Pacific Tracker 3.1 is comparable in features to the ASA24 software, which is most commonly used in the United States. [19] Importantly, the PacTrac 3.1 databases have been expanded with indigenous foods from other chemically analyzed data sources and from recipes provided by regional study participants for adults and children for use in analyzing diets from Pacific Island food cultures. For example, "banana" generates 22 matches in PacTrac 3.1, including BANANA GINGERBREAD (From DASH of Aloha), BANANA LUMPIA (GUAMANIAN), BUNELOS AGA (BANANA DOUGHNUTS) (GUAMANIAN), and MADOYA (FRIED BANANAS) (GUAMANIAN). Database entries and recipe calculations align with Food Composition table development guidance used by USDA and INFOODS food composition developers.

Dietary output from PacTrac 2.0 was shown to be associated with child blood pressure.[11] Further study to validate analysis of dietary records and dietary recalls using the PacTrac 3.1 tool with biomarkers would be a valuable endeavor, as has been recently done with the ASA24.[20]

Creation of the PacTrac database has involved the work of the many collaborators, including the HLPI Initiative, the Pacific Kids DASH for Health program, and the CHL program. These contributors include programmers, statisticians, nutritionists and physical activity experts to create a tool to analyze diet and physical activity of children and adults in the USAP Region. This core information is needed for association of diet with health and disease to advance science and develop program and policy guidance.

## Conclusions and Implications for Practice

Dietary and physical activity assessments for the US that include Native populations and children's foods and activities found in the USAP region are now possible using the PacTrac 3.1. This tool can be used by consumers, dietitians, and researchers to analyze the diet and physical activity of children and adults in the Pacific region. Availability of PacTrac 3.1 provides an instrument to identify healthy local cultural foods and food patterns, to be incorporated into program and policy guidance.

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# The Tantalizing Toxins of Tantalus, A Brief Review of Select Natural Poisons of O'ahu

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In the book *Micro*, Michael Crichton and Richard Preston describe natural ways to die on the island of O'ahu. In particular, the authors describe a detailed process by which the main characters devise their own "curare" from the poisons of the *Strychnos nux-vomica*, yellow oleander, and chinaberry plants to defend themselves against wild creatures.[1] Of course, this is adventure science fiction writing - meant to stir the imagination while using enough fact to make it believable - but the book does beg the question: how toxic are the flora and fauna of O'ahu? The authors did substantial research (as evidenced by a thorough bibliography) and highlighted some of the toxic plants - native or introduced - of the Hawaiian Islands. But how much reality lies within the science fiction of the story? Do humans need to be worried about the toxicity from these natural sources? How important is it to consider exposure to natural toxins when evaluating patients with concerning symptoms? In a brief overview, this article focuses on some of those poisons that innocuously live alongside us in the Aloha State.

One of the oldest and most classic toxins, strychnine, comes from multiple sources, particularly *S. nux-vomica* - a dense, deciduous tree with orb-like berries and characteristically flat seeds that was introduced to the Hawaiian Islands by the first physician at Queen's Medical Center, Dr. William Hillebrand.[2] (Figure 1). The knowledge of this plant and its toxin date back long before Dr. Hillebrand brought it to Hawai'i, and were likely the reason he included it in the botanical specimen collection he kept while living on the islands. The plant has long been used for its natural compounds in medicinal and nefarious ways, including in traditional Chinese medicine and in famous poisonings from the Victorian era.[3,4] However, it was not until 1818, that the specific alkaloid now known as strychnine was isolated by the chemists Pierre Joseph Pelletier and Joseph Bienaimé Caventou, leading to a widespread use of the compound for pest control and medicine.[5] Due to the alkaloid's perceived stimulant effects, the extract of the "strychnine tree" was often cited as a useful cardiac, respiratory, and digestive stimulant, an antidote to barbiturates, and a treatment for opioid overdoses.[6] Sports figures used it to obtain competitive advantage, including the winner of the 1904 Olympic Marathon who was accused of using an elixir of brandy and strychnine.[7,8] Between 1926 and 1928, an estimated three Americans per week died from strychnine toxicity, either by accident or murderous intent. In 1932, it was the most common cause of childhood poisoning. Most recently, the toxin is an adulterant of recreational drugs, commonly used to lace or bulk cocaine, heroin, and amphetamines.[6,9] The drugs remained on the market for many years. Even by 1946, when the organic chemist Sir Robert Robinson finally determined the structure of strychnine in his Nobel Prize-winning research on alkaloids, the true mechanism of strychnine was not fully

Figure 1. *Strychnos nux-vomica* Tree from Foster Botanical Garden (photo credit H. Keahi Mookini Horowitz)

understood.[10] Soon after Dr. Robinson's discovery, Dr. Robert B. Woodward and colleagues received the 1954 Nobel Prize for their research on synthesizing strychnine, marking a giant step forward in synthetic chemistry and broadening the understanding of the compound.[7,11] This new appreciation of strychnine eventually allowed for evaluation of its function. When ingested, inhaled, or otherwise introduced into the body, strychnine targets and inhibits the glycine receptors of the Renshaw interneurons of the nervous system. As a result, there is a loss of the normal inhibitory control performed by the Renshaw cells, leading to disinhibited and prolonged motor neuron activity.[6] Within 15-30 minutes of ingestion, patients may subsequently develop the characteristic tetanic-like posturing (opisthotonos) in response to even minor stimuli. The repeated muscle excitation can lead to hyperthermia, muscle breakdown such as rhabdomyolysis, and even seizures. Death often results from respiratory failure secondary to spastic contraction of the respiratory muscles.[9] Perhaps most alarmingly, the patient remains aware of all these symptoms as they progress. As such, it is important to control symptoms immediately with supportive care, benzodiazepines (often in high doses), and isolating the patient in a dark, low-stimulus environment, preferably in the intensive care unit. Given the risk for respiratory failure, there should be low threshold for sedation, intubation, and mechanical ventilation.[6,9] With regards to *S. nux-vomica* itself (unlike other sources of strychnine), the plant also contains brucine, which is structurally similar to strychnine and exerts similar effects.[6] Thus, this apparently innocuous plant has two lethal toxins hidden in the berries and bark that can prolonging or worsening its toxicity. So, should a patient present with tetanic-like spasms, it is important to keep the differential diagnosis broad and inquire about recent exposures to or ingestions of this toxic plant.

The second toxic plant highlighted in the book is yellow oleander (*Thevetia peruviana*), a relatively common plant with a characteristic spiraling, trumpet-shaped yellow flower that is typically found in tropical regions and often cultivated as an ornamental shrub (Figure 2). Despite its attractive outward appearance, nearly every part of the plant contains thevetin, thevetoxin, and other naturally occurring cardiac glycosides.[12] At one point in history, yellow oleander was utilized to treat heart failure, Hansen's disease, malaria, ringworm, and indigestion.[13] However, due to its significant gastrointestinal side effects (ie nausea and vomiting), its use gradually decreased, particularly as other drugs were introduced to the market.[12] However, yellow oleander remained an important agricultural plant for pest control and has even been investigated for potential chemotherapeutic effects.[14] Beyond its aesthetic appeal, yellow oleander is famous for its toxicity, especially for suicide and suicide attempts - a reputation that has garnered it the nickname of the "Be Still Tree" (Figure 3). From multiple reports, ingestion of even 8-10 seeds can be fatal, but most agree that

Figure 2. Flowers of the *Thevetia peruviana* (Yellow Oleander) from Foster Botanical Garden (photo credit: H. Keahi Mookini Horowitz)


Figure 3. "Be-Still Tree" Plaque of *Thevetia peruviana* (Yellow Oleander) from Foster Botanical Garden (photo credit: H. Keahi Mookini Horowitz)

the amount of glycoside absorbed is widely variable based on how it is consumed and what part of the plant is ingested.[13,15-17] Shortly after ingestion, patients start to experience gastric upset, nausea, vomiting, and then progress to weakness, cardiac dysrhythmias, possibly neurologic symptoms, and eventually death.[12] Like digoxin (arguably the most well-known and most used cardiac glycoside), the toxins of yellow oleander act to competitively bind and inactivate sodium-potassium exchangers (Na/K ATPases) on muscle cells.[18] This results in two main pathogenic pathways. First, the inhibition of sodium exchange results in increased intracellular sodium, activating a sodium-calcium exchange enzyme. Intracellular calcium then increases, leading to depolarization of the cell and activation of intracellular secondary messenger cascades. Gastric motility, cardiac conduction, and cardiac and other muscle contractility becomes quickly abnormal, resulting in the symptoms above. Second, the inhibition of potassium exchange results in hyperkalemia, hyperpolarizing muscle cells, leading to muscular weakness and cardiac dysrhythmias.[12,18] Symptoms may start as soon as 3 hours after ingestion. Unfortunately, the patient's symptoms may be so severe at initial presentation that they would be unable to provide any history of ingestion or exposure. Unless there is sufficient information, it is critical to suspect yellow oleander toxicity alongside digoxin toxicity in patients who come from areas where the plant is available and have signs and symptoms of cardiac glycoside toxicity. Treatment is largely supportive, with close attention to electrolyte abnormalities, cardiac dysrhythmias, and hemodynamic instability. Close cardiac monitoring is essential with particular attention to when to administer atropine in bradycardic and hypotensive patients and when to intervene on tachyarrhythmias, especially ventricular tachycardia.[18] For this same reason, correction of hyperkalemia is potentially lifesaving. Digoxin immune Fab fragments can also be tried for toxic ingestions of oleander as there may be some cross reactivity. [12,18]

Chinaberry (*Melia azedarach*) is commonly used in traditional Chinese medicine as antiparasitic or antifungal and represents an uncommon cause of human toxicity. However, in *Micro*, it becomes an essential component of the curare the adventurers concoct to defend themselves in the wilderness on Tantalus.[1] Meliatoxin from the fruit and toosendanin from the bark of the chinaberry tree are both limonoid tetranotriterpenes whose mechanism of action is still poorly understood but have known toxicity in many animals. Intoxicated animals often experience gastric upset, dry mouth, nausea, vomiting, and general agitation. However, in more extreme causes, more severe symptoms have been noted, including arrhythmias, hypotension, respiratory depression, cyanosis, blurred vision, perioral or extremity numbness, generalized weakness, inability to masticate and swallow, ataxia, loss of reflexes, seizures, and progression to respiratory arrest and death.[19] Unfortunately, without a clear understanding of the toxic mechanism of action of this plant there has been no elucidated antidote, so supportive care remains the mainstay of therapy. Diagnosis relies heavily on history of exposure and ingestion, which may often be incidental given the bright and potentially enticing appearance of the fruit itself. Close monitoring for decompensation is important, but severe human toxicity is rare.[19]

With equal parts work and imagination, the island of O'ahu yields an impressive bounty of toxins, and, certainly the toxic compounds discussed above have clinical implications. As such, toxins should remain a consideration for clinicians encountering patients with any risk of exposure and self-harm attempts. The true clinical threat remains more science fiction than fact, as rates of ingestion and exposure to these toxins are infrequent. Still, one cannot deny the potential danger that lurks in the forests of O'ahu, giving a whole new meaning to *mālama 'āina* (to care for the land).

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# Hawai'i Journal of Health & Social Welfare (HJH&SW)

## Guidelines for Publication of HJH&SW Supplements

The Hawai'i Journal of Health & Social Welfare (HJH&SW) partners with organizations, university divisions, and other research units to produce topic-specific issues of the journal known as supplements. Supplements must have educational value, be useful to HJH&SW readers, and contain data not previously published elsewhere. Each supplement must have a sponsor(s) who will work with the HJH&SW staff to coordinate all steps of the process. Please contact the editors at hjhsw@hawaii.edu for more information if you would like to pursue creating a supplement.

The following are general guidelines for publication of supplements:

1. Organizations, university divisions, and other research units considering publication of a sponsored supplement should consult with the HJH&SW editorial staff to make certain the educational objectives and value of the supplement are optimized during the planning process.

2. Supplements should treat broad topics in an impartial and unbiased manner. They must have educational value, be useful to HJH&SW readership, and contain data not previously published elsewhere.

3. Supplements must have a sponsor who will act as the guest editor of the supplement. The sponsor will be responsible for every step of the publication process including development of the theme/concept, peer review, editing, preliminary copy editing (ie, proof reading and first round of copy editing), and marketing of the publication. HJH&SW staff will only be involved in layout, final copy editing and reviewing final proofs. It is important that the sponsor is aware of all steps to publication. The sponsor will:

a. Be the point of contact with HJH&SW for all issues pertaining to the supplement.
b. Solicit and curate articles for the supplement.
c. Establish and oversee a peer review process that ensures the accuracy and validity of the articles.
d. Ensure that all articles adhere to the guidelines set forth in journal's Instructions to Authors page, especially the instructions for manuscript preparation and the statistical guidelines.
e. Obtain a signed Copyright Transfer Agreement for each article from all authors.
f. Comply with all federal, state, and local laws, rules, and regulations that may be applicable in connection with the publication, including ensuring that no protected health information appears in any article.
g. Work with the editorial staff to create and adhere to a timeline for the publication of the supplement.
h. Communicate any issues or desired changes to the HJH&SW staff in a timely manner.

4. Upon commissioning a supplement, the sponsor will be asked to establish a timeline for the issue which the sponsor and the HJH&SW editor(s) will sign. The following activities will be agreed upon with journal publication to take place no later than 24 months after signing. Extensions past the 24 months will be subject to additional fees based on journal publication rates at that time:

- Final date to submit a list of all articles, with working titles and authors
- Final date for submitting Word documents for copy editing
- Final date for submitting Word documents for layout
- Final date to request changes to page proofs (Please note that changes to page proofs will be made only to fix any errors that were introduced during layout. Other editing changes will incur an additional fee of $50 per page.)

5. The cost of publication of a HJH&SW supplement is $5,000 for an 8-article edition with an introduction from the sponsor or guest editor. Additional articles can be purchased for $500 each with a maximum of 12 articles per supplement. This cost covers one round of copy editing (up to 8 hours), layout, online publication with an accompanying press release, provision of electronic files, and indexing in PubMed Central, SCOPUS, and Embase. The layout editor will email an invoice for 50% of the supplement to the designated editor for payment upon signature of the contract. The remaining will be due at the time of publication. Checks may be made out to UCERA.

6. The sponsor may decide to include advertisements in the supplement in order to defray costs. Please consult with the HJH&SW advertising representative Michael Roth at 808-595-4124 or email rothcomm@gmail.com for assistance.

7. Supplement issues are posted on the HJH&SW website (http://www.hawaiijournalhealth.org) as a full-text PDF (both of the whole supplement as well as each article). An announcement of its availability will be made via a press release and through the HJH&SW email distribution list. Full-text versions of the articles will also be available on PubMed Central.

8. It is the responsibility of the sponsor to manage all editorial, marketing, sales, and distribution functions. If you need assistance, please contact the journal production editor. We may be able to help for an additional fee.

9. The editorial board reserves the right of final review and approval of all supplement contents. The HJH&SW will maintain the copyright of all journal contents.

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**Sample Workflow and Timeline for a Supplement**

1. The sponsor contacts the HJH&SW editors (hjhsw@hawaii.edu) to discuss the supplement topic, estimated timeline, length and cost. HJH&SW staff will review the journal requirements for articles and share our review process with the sponsor. **Time frame: 2 weeks**

2. The sponsor will complete the draft contract and pay a non-refundable deposit of $2500 or half the contract value. **Time frame: 3 days**

3. The sponsor will solicit articles for the supplement. **Time frame: 3-6 months**

Articles must comply with:

- Instructions for Manuscript Preparation and Submission of Research Articles
- Instructions for Manuscript Preparation and Submission of Columns
- HJH&SW Statistical Guidelines
- HJH&SW Style Guide for Native Hawaiian Words and Phrases
  AMA Manual of Style A free summary can be found here.

4. The sponsor will oversee the article selection, peer review, and editing process. We recommend that time be allowed for at least two rounds of reviews for each article. **Time frame: 3-6 months**

- Ensure that each article includes Institutional Review Board (IRB) review and approval, and a statement disclosing any conflicts of interest.
- Obtain a Copyright Transfer Agreement signed by all authors for each article.

5. *Optional*: During this time, the sponsor can solicit advertisements for the supplement to help defray costs for publication and/or printing. To initiate this process, the sponsor will work the HJH&SW advertising representative Michael Roth at 808-595-4124 or rothcomm@gmail.com.

6. The sponsor or their designee will conduct a final review of each article to ensure adherence to HJH&SW guidelines and AMA style. **Time frame: 2 weeks**

7. For each article, the sponsor will submit the final Word document and Copyright Transfer Agreement to the HJH&SW journal production editor. The journal production editor will send the articles to the copy editor for final journal style review. Copyediting will be 8 hours per edition plus 1 hour per article for additional articles purchased. Any additional hours will be billed at $100 per hour. **Time frame: 2 weeks**

8. The sponsor will submit the final articles to the layout editor for formatting. **Time frame: 1 month**
Acting in the role of guest editor, the sponsor will include a column introducing the supplement.
**IMPORTANT:** All articles submitted for layout should be in their finalized form. Page proofs will be returned to the sponsor for their review and approval, but changes will only be made to fix any errors that were introduced during the layout process. Any editing or changes to the text or figures after the initial copy layout will incur a fee of $50 per page.

9. The sponsor will review the electronic copy from the layout editor and submit any final corrections. **Time frame: 5 working days**

10. The layout editor will make the final corrections and provide a finished electronic copy of the supplement to the sponsoring editors to allow time for printing.

11. The managing editor will work with the sponsor to draft a press release. Sponsors should contact the managing editor at least 30 days prior to the date of publication to plan and script the press release. Sponsors are encouraged to submit 1-2 photos to accompany the press release. Note that obtaining signed photo releases is the responsibility of the sponsor.

12. The supplement will be published online along with the press release. An electronic copy will be sent to our subscribers and circulation lists, and the edition will be forwarded to the National Library of Medicine for indexing and made available for no cost access to the public.

Revised 2/6/20

# Hawai‘i Journal of Health & Social Welfare (HJH&SW)

## Style Guide for the Use of Native Hawaiian Words and Diacritical Markings

The HJH&SW encourages authors to use the appropriate diacritical markings (the ‘okina and the kahakō) for all Hawaiian words. We recommend verifying words with the Hawaiian Language Dictionary (http://www.wehewehe.org/) or with the University of Hawai‘i Hawaiian Language Online (http://www.hawaii.edu/site/info/diacritics.php).

Authors should also note that Hawaiian refers to people of Native Hawaiian descent. People who live in Hawai‘i are referred to as Hawai‘i residents.

Hawaiian words that are not proper nouns (such as *keiki* and *kūpuna*) should be written in italics throughout the manuscript, and a definition should be provided in parentheses the first time the word is used in the manuscript.

Examples of Hawaiian words that may appear in the HJH&SW:

| | |
|---|---|
| ***‘āina*** | ***Mānoa*** |
| ***ali‘i*** | ***Māori*** |
| ***Hawai‘i*** | ***Moloka‘i*** |
| ***kūpuna*** | ***O‘ahu*** |
| ***Kaua‘i*** | ***‘ohana*** |
| ***Lāna‘i*** | ***Wai‘anae*** |

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