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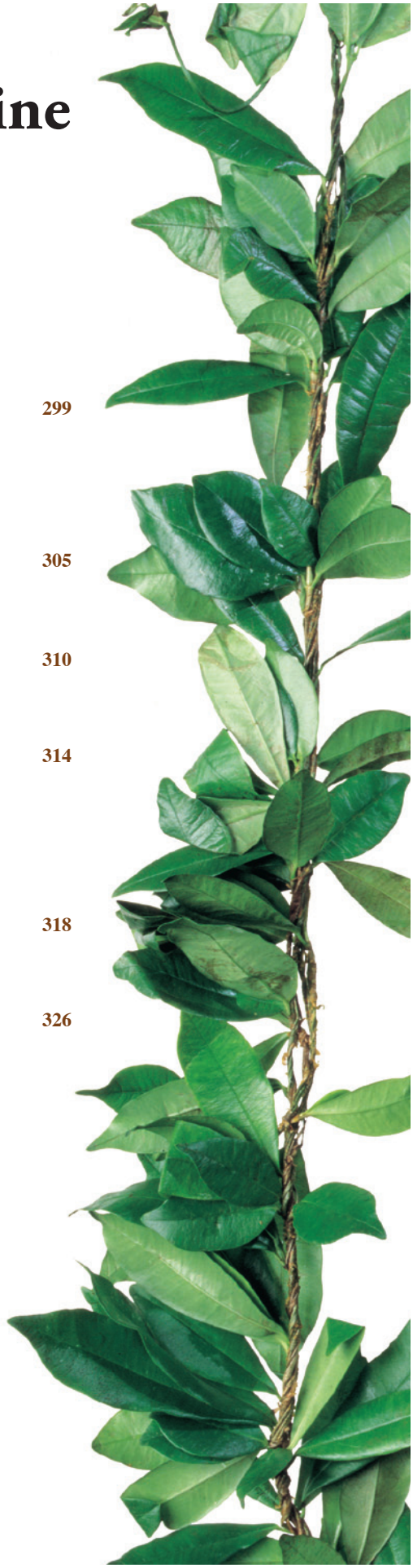

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The Hawai‘i Journal of Medicine & Public Health was formerly two separate journals: The Hawai‘i Medical Journal and the Hawai‘i Journal of Public Health. The Hawai‘i Medical Journal was founded in 1941 by the Hawai‘i Medical Association (HMA), which was incorporated in 1856 under the Hawaiian monarchy. In 2009 the journal was transferred by HMA to University Health Partners of Hawai‘i (UHP Hawai‘i). The Hawai‘i Journal of Public Health was a collaborative effort between the Hawai‘i State Department of Health and the Office of Public Health Studies at the John A. Burns School of Medicine established in 2008.

D. Varez

Physician Adherence to Sexually Transmitted Infection Screening Guidelines in an OB/GYN Teaching Clinic in Hawai'i

Alyssa Dee P. Carlson MPH; Mary Tschann PhD, MPH; Somsook Santibenchakul MD, MPH; Eric L. Hurwitz DC, PhD; and Jennifer Salcedo MD, MPH, MPP

Abstract

Rates of chlamydia (CT) and gonorrhea (GC) have risen for the first time in the United States since 2006. Certain population groups are disproportionately affected by these sexually transmitted infections (STIs) as well as HIV. The Centers for Disease Control and Prevention (CDC) and professional societies have published screening guidelines for these STIs for women under the age of 25. We aimed to quantify physician adherence to GC/CT and HIV screening guidelines and to determine demographic factors associated with GC/CT and HIV screening recommendations among women 14-25 years old in Honolulu, Hawai'i. We conducted a retrospective chart review of all visits to an OB/GYN teaching clinic in 2014 to determine rates of STI screening recommendations and evaluate differences in screening recommendations by demographic factors such as patient age, race, insurance type, visit type, and visit number during the study period. Electronic medical records of 726 visits by 446 patients were reviewed. Among visits by patients with indications for screening, 71.0% and 21.6% received screening recommendations for GC/CT and HIV, respectively. Age group, race, and visit type were significantly associated with receiving screening recommendations. A lack of appropriate documentation regarding the assessment of risk factors for GC/CT and HIV screening was observed. Emphasis should be placed on more thorough ascertainment and documentation of patients' risk factors for STI acquisition to determine screening needs at each clinical visit based on professional guidelines, as substantial public health benefits may be gained through the identification and prompt treatment of GC/CT and HIV infections.

Keywords

chlamydia, gonorrhea, HIV, sexually transmitted infection, screening, Hawai'i, adolescent, resident physician

Abbreviations

CDC – Centers for Disease Control and Prevention
CT – chlamydia
EHR – electronic health record
GC – gonorrhea
HIV – human immunodeficiency virus
NHOPI – Native Hawaiian and other Pacific Islander
STI – sexually transmitted infection

Introduction

In 2014, rates of chlamydia (CT) and gonorrhea (GC) infections rose for the first time since 2006 in the United States (U.S.).[1] Surveillance data from the Centers for Disease Control and Prevention (CDC) demonstrated a CT rate increase of 2.8% in 2014 (456.1 cases per 100,000, compared to 443.5 cases per 100,000 in 2013). The GC rate increased from the previous year by 5.1% (110.7 cases per 100,000 compared to 105.3 cases per 100,000 in 2013).[1] These sexually transmitted infections (STIs) disproportionately affect young people and people of color.[2] In 2014, 66% of all CT cases were found in young people aged 15-24, despite this group comprising less than 14% of the total U.S. population.[2,3] Furthermore, national incidence rates of chlamydia infections among Native Hawaiian and other Pacific Islander (NHOPI) populations were 3.5 times greater than among Whites and 5.7 times greater than among Asians in 2013. Similarly, gonorrhea incidence among NHOPI were 2.7 times greater than Whites in the U.S.[4] In the same year, Hawai'i, the state with the largest percentage of these racial groups, had higher reported rates of CT infection than the national average, ranking 15th among the 50 states.[5,6] Although national Human Immunodeficiency Virus (HIV) incidence has declined since 2005, and the incidence in Hawai'i is relatively low (38th among the 50 states), the life-threatening consequences of this infection underscore the importance of routine screening.[6-9]

Chlamydia, gonorrhea and HIV infections are frequently asymptomatic, and untreated infections may have severe long-term health consequences. Among women, chlamydial and gonorrheal infections increase the risk of pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain, and infertility, and undiagnosed and untreated HIV can progress to Acquired Immune Deficiency Syndrome (AIDS).[7-11] Unrecognized transmission of these infections to sexual partners is a substantial public health concern. It is for these reasons that the CDC and the U.S. Preventative Services Task Force (USPSTF) recommend annual chlamydia and gonorrhea screening for all sexually active women under 25 years of age, with additional screening when new risk factors are identified.[12,13] These risk factors include new or multiple partners, having a partner with a sexually transmitted infection, having a partner with concurrent partners, or having symptoms of infection. All persons aged 13-64 are recommended to receive HIV screening at least once in their lives, and more frequently for risk factors such as unprotected sex or use of injection drugs.[14] Despite clear guidelines for routine GC/CT and HIV screening, many physicians do not routinely recommend such testing, and less than half of all sexually active women under 25 years of age reported having been screened for an STI in 2009.[15] Each clinical visit is an important opportunity to assess new or continuing risk factors for GC/CT and HIV and to make appropriate recommendations for testing, as patients may present with additional indications at any time and may not present for scheduled preventive health visits. Thorough documentation of this information, as well as testing history, are critical to the provision of high quality reproductive health care in this age group with documented disparities in the incidence of sexually transmitted infections.

The purpose of this study is to (1) quantify physician adherence to GC/CT and HIV screening guidelines (2) quantify the

proportion of patient visits in which recommended screening was received, and (3) identify demographic factors associated with GC/CT and HIV screening recommendations among visits by women 14-25 years old to an outpatient obstetrics and gynecology (OB/GYN) resident clinic in Honolulu, Hawai'i.

Methods

We conducted a retrospective chart review of all patient visits by non-pregnant women ages 14-25 years at a single outpatient OB/GYN resident clinic in 2014. Researchers reviewed resident and attending physician notes, problem list tabs, laboratory tests ordered and conducted, and scanned media files of testing received outside of our health system in each respective electronic health record (EHR). Women with a minimum age of 14 were included in the review as this is the age at which patients are able to provide consent for reproductive health services in Hawai'i.[16] Pregnant women were excluded from the study as they are a special population with unique STI screening recommendations.[11] Some patients were seen more than once during the study period and each visit was viewed as a unique encounter and recorded independently, as new or additional STI risk factors may have been reported during subsequent visits during the study period. Demographic variables contained within the EHR such as age, race, insurance type, visit type, and number of clinic visits within the study period were collected. Age was recorded as a dichotomous variable, 14-19 or 20-25 years. This was to facilitate comparison of outcomes between patients considered adolescent (14-19) and young adult (20-25). The study was approved by the Hawai'i Pacific Health Research Institute and the Western Institutional Review Board (WIRB Protocol # 20150630).

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). The primary outcome variable was a documented recommendation for GC/CT screening by a resident or attending physician among patients indicated for screening per CDC/USPSTF guidelines. Indications for GC/CT screening were defined as: lack of documented history of GC/CT testing in the prior 12 months (if sexually active), or the presence of new risk factors, including new or multiple partners, symptoms potentially indicative of an STI, a positive test for another STI since last testing, a partner with positive test for any STI since last testing, or concern that a sexual partner had new concurrent partners since last testing. Patients with a documented GC/CT test within the past 12 months, but without explicit documentation of the presence or lack of risk factors at the current visit, were categorized as "indication not documented". Patients without a documented GC/CT test within the past 12 months were categorized as indicated for GC/CT screening at the current visit (Figure 1). An additional study outcome was a documented recommendation for HIV screening among patients with indications for screening. Indications for HIV screening included: never having been screened for HIV (if sexually active) or the presence of new risk factors such as diagnosis of an STI since last testing, unprotected sex since last testing, having a partner with an STI since last testing, new or multiple partners, injection drug use by self or partner, or having a partner with new or concurrent partners since last testing. Patients with lack of documentation of ever receiving an HIV test were categorized as indicated for HIV screening at the current visit (Figure 2). The secondary study outcome was documentation of GC/CT and/or HIV testing having been performed when recommended by a physician. This was determined by reviewing laboratory tests, and scanned media results from testing conducted in other facilities, within the medical record.

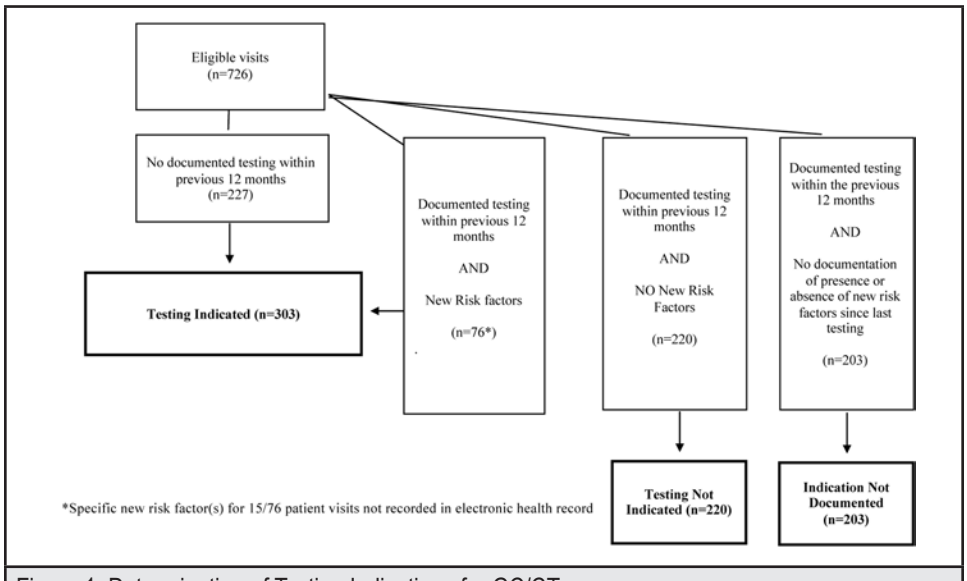

Figure 1. Determination of Testing Indications for GC/CT

To identify factors potentially associated with GC/CT and HIV screening recommendations, Chi-square tests of independence or Fisher's exact tests (when n<5), and bivariable generalized linear models with logit link functions were employed among all demographic variables collected. Potentially significant variables (P<.1) were then examined using a multivariable generalized linear model, with a logit link function, to identify associations after controlling for other factors.

Results

A total of 1,039 clinic visits by non-pregnant women aged 14-25 in 2014 were initially reviewed. Of those visits, 313 were excluded due to self-reported virginal status documented in the medical record, a new diagnosis of pregnancy, or receipt of only ancillary services (such as a vaccination or pregnancy test not including interaction with a physician), resulting in 726 remaining visits among 446 patients with potential indications for STI screening. Indications for GC/CT and HIV screening were present in 41.7% (303 visits among 192 patients) and 42.1% (306 visits among 188 patients) of all eligible visits, respectively. The majority of unique patients with indications for GC/CT and/or HIV screening were Asian or Native Hawaiian and seen once during the study period. Medicaid was the most common payer in this population (Table 1).

GC/CT Screening Recommendations

Three hundred and three visits, representing 192 unique patients, had an indication for GC/CT screening. Recommendations for screening were documented in 71.0% (215) of all indicated patient visits. When recommended during the visit, GC/CT screening was conducted at a rate of 85.6% (184), while screening was not completed at a rate of 14.4% (31). Among visits in which recommended testing was not completed, 45% (14) of patients declined and for 55% (17) of patients, the medical record contained no documented reason for why testing wasn't performed. Among those tested, 6% (11) of tests returned positive for CT. No positive GC tests were reported.

Bivariate analyses evaluating the association between testing recommendations among indicated patients and demographic variables revealed a significant association with age group (P<.0001), race, (P<.0001), insurance type (P<.0001), visit type (P=.0039), and visit number (P<.0001). The multivariable model demonstrated a higher likelihood of receiving a recommendation for indicated GC/CT screening among visits scheduled as annual gynecologic preventive care exams, after adjusting for the effects of age group, race, insurance type, and visit number (Adjusted Odds Ratio [aOR]:7.61 95% CI: 3.65-16.66) (Table 2). All other covariates were found to be statistically non-significant.

HIV Screening Recommendations

Three hundred and six patient visits, representing 188 unique patients, had an indication for HIV screening. Among those patient visits, 21.6% (66) resulted in a recommendation for screening. When recommended, HIV testing was completed 42% (28) of the time. Among visits in which testing was not completed, 58% (22) of patients declined, 37% (14) were referred elsewhere for testing, and for 5% (2) of patients there were no documented reasons for why testing wasn't performed. All HIV tests resulted as negative.

Bivariable analyses evaluating the potential associations between screening recommendations among indicated patients and demographic variables revealed significant associations with age group (P<.0001), race (P<.0001), insurance type (P<.0001), visit type (P<.0001, and visit number (P<.0001). The multivariable model demonstrated a significantly greater likelihood of receiving a recommendation for HIV testing when indicated among patients who were Native Hawaiian or Other race, adolescent, or were presenting for an annual exam (Table 3).

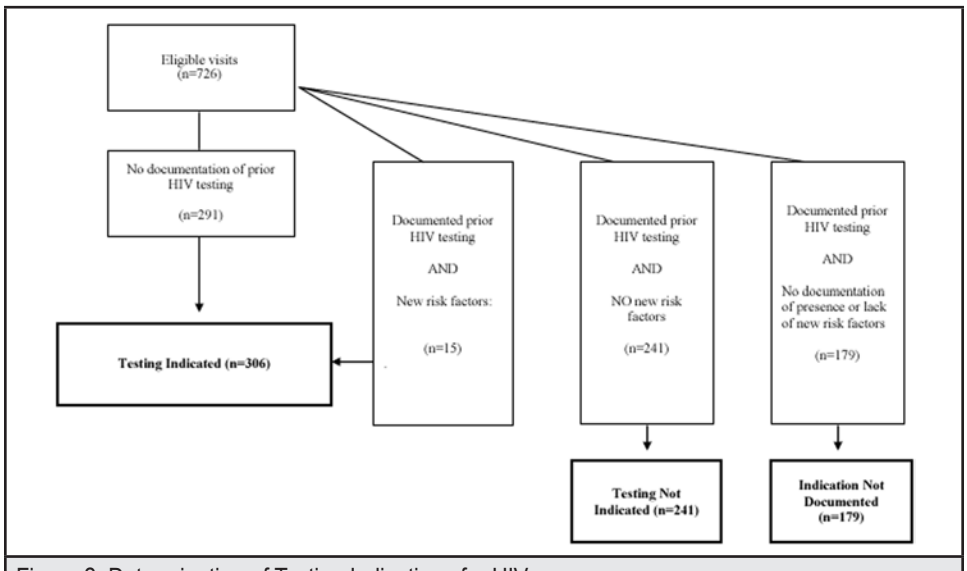

Figure 2. Determination of Testing Indications for HIV

Table 1. Patient Demographics: Demographics of unique patients with visits that included indications for GC/CT screening (n=192) and HIV screening (n=188)

	Patients with GC/CT testing indication (n=192)	Patients with HIV testing indication (n=188)
Age Group		
14-19	80 (42%)	95 (51%)
20-25	112 (58%)	93 (49%)
Race		
Asian	61 (32%)	62 (33%)
Native Hawaiian	63 (33%)	46 (24%)
Other	16 (8%)	16 (9%)
Pacific Islander	21 (11%)	22 (12%)
White	31 (16%)	42 (22%)
Insurance*		
Clinic subsidized visit	13 (7%)	16 (8%)
Federal	4 (2%)	5 (3%)
None	29 (15%)	37 (20%)
Private	40 (21%)	42 (22%)
Public	106 (55%)	88 (47%)
Visit Type**		
Annual Exam	80 (42%)	56 (30%)
Gynecological Care	105 (55%)	131 (69%)
Postpartum Exam	7 (3%)	1 (1%)
Visit Number		
Visited once	140 (73%)	129 (69%)
Visited twice	37 (19%)	43 (23%)
Visited 3 or more times	15 (8%)	16 (8%)

*Federal = coverage received by members of the military or their dependents , as well as some federal civilian employees
Public = coverage provided by state government programs, such as Medicaid/Quest
**Initial visit type among patients who were seen more than once during the study period

Table 2. GC/CT Screening Recommendations Bivariable and Multivariable Analysis: Unadjusted and adjusted* odds ratios (aOR) and 95% confidence intervals (CIs) of receiving recommendations for GC/CT among indicated visits (n=303)

	OR	95% CI	aOR	95% CI
Age Group				
14-19	0.91	0.55-1.51	1.30	0.64-2.39
20-25	Ref.	Ref.	Ref.	Ref.
Race				
Asian	**0.38**	**0.14-0.93**	0.53	0.71-1.48
Native Hawaiian	0.41	0.15-1.01	0.66	0.19-1.85
Other	0.65	0.18-2.32	1.12	0.24-4.62
Pacific Islander	**0.31**	**0.11-0.92**	0.59	0.27-2.1
White	Ref.	Ref.	Ref.	Ref.
Insurance				
Clinic subsidized visit	1.78	0.57-5.61	1.91	0.53-6.89
Federal	2.85	0.34-24.25	1.70	0.18-17.12
None	1.64	0.73-3.66	1.37	0.51-3.69
Private	1.33	0.67-2.63	1.38	0.64-2.98
Public	Ref.	Ref.	Ref.	Ref.
Visit Type				
Annual Exam	**9.03**	**3.51-15.63**	**7.61**	**3.48-16.66**
Gynecological Care	Ref.	Ref.	Ref.	Ref.
Postpartum Exam	**0.32**	**0.11.0.89**	0.34	0.11-1.05
Visit Number				
1	Ref.	Ref.	Ref.	Ref.
2	0.68	0.36-1.26	0.96	0.48-1.90
3+	1.02	0.41-2.54	1.58	0.59-4.22

*Adjusted for age group, race, insurance, visit type, and visit number

Table 3. HIV Screening Recommendations Bivariable and Multivariable Analysis: Unadjusted and adjusted* odds ratios (aOR) and 95% confidence intervals (CIs) of receiving recommendations for HIV testing among indicated visits (n=306)

	OR	95% CI	aOR	95% CI
Age Group				
14-19	**5.92**	**2.67-13.09**	**5.66**	**2.29-14.02**
20-25	Ref.	Ref.	Ref.	Ref.
Race				
Asian	**3.61**	**1.16-11.20**	2.95	0.87-10.07
Native Hawaiian	**5.85**	**1.90-18.01**	**4.80**	**1.41-16.32**
Other	**4.50**	**1.15-17.67**	**4.44**	**1.00-19.77**
Pacific Islander	0.46	0.05-4.29	0.47	0.04-4.98
White	Ref.	Ref.	Ref.	Ref.
Insurance				
Clinic subsidized visit	1.75	0.70-4.40	1.47	0.50-4.32
Federal	0.49	0.06-4.08	0.59	0.05-6.65
None	0.29	0.08-0.99	0.56	0.14-2.19
Private	0.80	0.37-1.76	0.91	0.38-2.19
Public	Ref.	Ref.	Ref.	Ref.
Visit Type				
Annual Exam	1.4	0.73-2.68	**2.26**	**1.00-5.09**
Gynecological Care	Ref.	Ref.	Ref.	Ref.
Visit Number				
1	Ref.	Ref.	Ref.	Ref.
2	0.45	0.19-1.05	0.42	0.17-1.06
3+	0.38	0.11-1.32	0.33	0.09-1.23

*Adjusted for age group, race, insurance, visit type, and visit number
Note: Among 7 postpartum visits with indications for testing, no visits included a recommendation for HIV screening.

Discussion

While recommendations for GC/CT and HIV screening are clear for women under age 25, our study identified a significant gap in physician adherence to such guidelines in an OB/GYN teaching clinic. Specifically, GC/CT screening was not recommended in approximately 30% of visits in which it was indicated. Further, we identified a lack of adequate physician documentation regarding the presence of new risk factors for GC/CT and HIV infections in women who had documented testing in the past 12 months, or ever, respectively, which points toward the likelihood of an even higher rate of missed testing. However, when physicians recommended GC/CT screening, 85.5% of patients underwent testing during the visit. This highlights the importance of physician recommendations as an important link in ensuring adolescents and young adults receive appropriate STI screening, as well as patient willingness to be screened when prompted. In contrast, the majority of patient visits with indications for HIV screening did not include a recommendation for screening, and when prompted approximately half (58%) of patients declined screening at these visits. Further analysis should be conducted on motivators and barriers to HIV screening among this population.

Bivariable and multivariable modeling showed significant associations between the receipt of GC/CT screening recommendations among indicated patients and demographic factors. Although the effects of race were attenuated and no longer statistically significant after controlling for other factors, a decreased likelihood of receiving GC/CT screening recommendations among indicated Asian and Pacific Islander compared to White patients remained. These findings should be examined further in a larger sample through which more precise estimates may be ascertained. Having a visit scheduled as an annual gynecological preventative appointment was identified as the strongest predictor of receiving GC/CT and HIV screening recommendations in alignment with professional guidelines in this study. It is likely that physicians are attuned to addressing STI screening at these dedicated visits, however, interventions should be implemented to prompt screening during other types of scheduled visits. Visits by patients aged 14-19, Native Hawaiians or other race women, were more likely to receive appropriate HIV screening recommendations, which suggests a need to further evaluate factors influencing physician provision of testing recommendations.

Strengths of this study include that it is the first to analyze physician adherence to professional STI screening guidelines over a full calendar year in a population with nationally documented disparities in GC/CT incidence (Native Hawaiians and other Pacific Islanders)[4] in Hawai‘i. Despite having unique health experiences, NHOPI are commonly grouped into a single race category in national data. As Hawai‘i has the largest proportion of these racial groups in the nation, this clinic is an ideal setting to evaluate testing rates for these and other groups that are generally underrepresented nationally.[5] Additionally, we were able to assess actual tests conducted. This has not been possible in prior studies using administrative data such as

laboratory billing, or national surveys, which is unable to accurately differentiate between recommendations provided and testing conducted[19-22] Furthermore, the study site represents the primary OB/GYN resident training site in the State of Hawai‘‘i. Future physician interventions aimed at increasing physician adherence to STI screening guidelines would have substantial impacts on reproductive health practices in the state.

This study also has several limitations. First, the small number of observations available for some study outcomes (particularly HIV screening recommendations) reduced precision and limited our statistical power to detect associations between demographic factors and provision of testing recommendations. Additionally, physicians may have made recommendations for STI testing but failed to document them in the EHR, causing such recommendations to be missed if the tests were not ordered. Second, all GC/CT and/or HIV testing conducted at non-affiliated institutions may not have been captured in our study, particularly when such testing wasn't endorsed by patients. However, we consider our comprehensive review of notes (including patient self-report of prior screening), problem list tabs, and scanned media from outside facilities within the EHR to have optimized collection of this data. Third, additional risk factors for HIV screening such as intravenous (IV) drug use have not been routinely assessed in this setting, which may have led to an under recognition of HIV testing indications. Fourth, the results of this study may be limited in generalizability. The data originated from a single hospital-based clinic. A larger sample that includes males, private offices, and state-run clinics, and the collection of data that contains patients' motivations for accepting or refusing testing, may provide additional insights regarding trends in screening gaps among specific demographic groups. Lastly, patients were restricted from choosing multiple race categories for inclusion in the electronic health record. Allowing the selection of multiple races may influence the effect of race and ethnicity on GC/CT screening recommendations, as an estimated 23% of Hawai‘i residents self-identify with two or more races.[3]

In summary, among patient visits with a documented indication(s) for screening, 29.0% were not recommended for GC/CT screening and 78.4% were not recommended for HIV screening in this resident training clinic. Annual gynecologic preventive health visits were positively associated with receiving GC/CT and HIV screening recommendations. Groups such as women aged 14-19, Native Hawaiians, or other races had greater likelihood of receiving recommendations for HIV screening when indicated. Moving forward, emphasis should be placed on interventions aimed at increasing physician documentation of STI risk factors, and promoting screening at all clinical opportunities to increase adherence to screening guidelines, as substantial public health benefits may be gained through the identification and prompt treatment of GC/CT and HIV infections.

Conflict of Interest

None of the authors identify any conflicts of interest related to this publication.

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Patient Communication, Satisfaction, and Trust Before and After Use of a Standardized Birth Plan

Clare-Marie Anderson; Rosie Monardo MD; Reni Soon MD, MPH; Jennifer Lum MD; Mary Tschann MPH; and Bliss Kaneshiro MD, MPH

Abstract

The birth plan was developed as a way for pregnant women to communicate their desires and expectations for labor and delivery. Standardized birth plans have been used by some birth facilities as a communication tool. In this quality improvement project, we sought to describe communication, trust, and satisfaction scores after delivery in a group of patients who used a standardized birth plan. All pregnant women at 24 or more weeks of gestation were asked to complete a short, standardized birth plan. Communication, trust, and satisfaction were assessed before and after delivery. Descriptive analyses showed that communication, trust, and satisfaction scores were high following delivery. Scores for all three factors increased significantly following delivery though increases were modest. Most patients (84%) indicated they would use a birth plan with a subsequent delivery.

Keywords

birth plan, labor, delivery, satisfaction, trust, communication

Introduction

A birth plan outlines a woman's desires for the labor and delivery experience. Patients who use birth plans typically prepare a written document during the antepartum period, which they present to staff at the time of labor.[1] Birth plans address physical and emotional preferences and include items such as identifying support people who will be present at the delivery. Birth plans can also communicate a patient's preferences regarding medical interventions like epidurals and induction of labor. The use of patient-initiated birth plans is becoming increasingly common in obstetric care. Multiple online sites geared towards pregnant women include examples and templates of birth plans.

In addition to being a communication tool, birth plans have also been described as a way for women to exert more autonomy during the birth experience. Advocates of birth plans state that they allow women to feel empowered and less "out of control."[2] Increased patient involvement in obstetric decision-making increases satisfaction with the labor and delivery experience.[3,4] In one study, feeling left out of decision-making was associated with a six-fold decrease in satisfaction among nulliparous women and a 15-fold decrease in satisfaction among multiparous women.[5]

Whether a patient-initiated birth plan has an impact on obstetric outcomes remains unclear.[6] Medical personnel vary in their opinion of birth plans, with some who support birth plans and others who report that it sets unrealistic expectations for an unpredictable process.[7,8]

In contrast to patient-initiated birth plans, standardized birth plans are designed by health care providers to present women with a standard series of questions that allow them to delineate their wishes for labor and delivery. Standardized birth plans can be a simple way for health care providers to introduce birth plans to women who might not be familiar with this concept. Compared to the birth plans a woman might find on the internet, standardized birth plans can provide women with labor and delivery options available at a particular facility.

Use of a standardized birth plan in Australia increased satisfaction for patients and increased communication between patients and providers.[9] In that study, 95% of patients stated that they would encourage future birth plan use.[9] Another study conducted among low-income patients in Mexico showed that this population benefitted from standardized birth plans and would use them again.[7] In the current quality improvement project, we sought to describe how a group of culturally and educationally diverse women presenting for obstetric care in Honolulu, Hawai'i rated communication, satisfaction and trust with use of a standardized birth plan during labor and delivery.

Materials and Methods

This study was conducted at the Kapi'olani Medical Center Women's Outpatient Clinic in Honolulu, Hawai'i between September 1, 2014 and November 30, 2015. Patients were primarily cared for by the University of Hawai'i Obstetrics and Gynecology resident physicians at this clinic. We created a standardized birth plan based on options available to patients in our clinical setting (Table 1). The birth plan was two pages long and was designed to be at or below an eighth-grade reading level. Adult women who presented for obstetric care and could read and understand the birth plan in English without the assistance of a translator were eligible. Women who planned to have a cesarean delivery or anticipated delivering outside our facility were excluded. This project was designated as a quality improvement project by the Hawai'i Pacific Health Research Institute and was granted exempt status by the Hawai'i Pacific Health Research Institute.

Women who were at 24 or more weeks of gestation were approached by their physician about participating in this study. Written consent was obtained from those who wished to participate. Participants took the pre-delivery survey at one of their antepartum visits. They provided demographic information including age, education, race, and parity and were asked whether they had used a birth plan with any previous deliveries. Patients were asked "how satisfied do you think you will be with using a birth plan for the delivery of your baby, do you feel that you have adequate communication with your care team, and do you trust

Table 1. Standardized Birth Plan

My supportive person's first name: _____

For each statement, please choose ALL options that you would like.

While in labor, I would like:
___ Music playing with speakers that I provide
___ The TV playing
___ A quiet room
___ My support person to be present and be able to stay with me
___ To stay hydrated with clear liquids and ice chips

I would like to spend the early part of labor
___ Walking
___ Lying down
___ Take a shower

For pain relief, I would like to use
___ Breathing techniques
___ Visualization techniques
___ Meditation
___ Massage, as provided by my support person
___ Epidural
___ Local anesthetic at time of delivery (pudendal block)
___ I am not sure but will request what I would like at the time

As the baby delivers, I would like to
___ Push as directed by medical staff
___ Push when I feel like pushing
___ The labor room to be quiet
___ Use a mirror to see the baby deliver
___ To touch the baby's head as it crowns
___ To avoid episiotomy (a small cut of the outer vagina to make more room for baby) unless my doctor deems it necessary
___ To avoid operative delivery (forceps or vacuum to help the baby deliver) unless my doctor deems it necessary

Immediately after vaginal delivery, I would like:
___ The baby to be placed on my chest
___ The baby to be cleaned and swaddled before given to me
___ My support person to cut the umbilical cord
___ The umbilical cord to be cut after it stops pulsing, unless it is necessary for it to be cut sooner for the well-being of the baby.
___ To donate cord blood to the Hawai'i Cord Blood Bank
___ To see the placenta before it is discarded
___ To take the placenta home with me

If a Cesarean section is necessary, I would like
___ My support person to be present
___ My support person to hold the baby as soon as possible
___ My support person to accompany the baby to the nursery
___ To see the baby before it is taken to the nursery
___ To have the pediatric team update me before taking the baby from the operating room

I would like to breastfeed
___ As soon as possible after delivery
___ After the baby is cleaned and swaddled
___ I am not sure if I will breastfeed my baby
___ I am interested in seeing the lactation consultant while I am in the hospital
___ I would only like to feed my baby formula if recommended by the pediatricians
___ I would like access to a breast pump

the doctors taking care of you?" Patients responded by marking a position on a 10-centimeter line based on the strength of their feelings of satisfaction, communication, and trust. This visual analog scale enabled the patients' answers to be quantified by equating their response to each question to a number out of 10. After answering questions about communication, satisfaction, and trust, patients were presented with the standardized birth plan and were allowed to make their choices independently. Resident physicians then reviewed the birth plan with women and answered questions about the birth plan. Completion of the birth plan took less than 10 minutes for most patients.

Birth plans were entered into the electronic medical record so that they could be accessed at the time of admission to labor and delivery. Following delivery, a second survey using identical questions and a 10-centimeter visual analog scale was administered before hospital discharge by a research assistant who was not involved in the care of the patient. Following discharge from the hospital, an investigator reviewed the patient's medical record and noted gestation age at the time of delivery, any obstetric events such as the need for induction or cesarean section, as well as any obstetric or neonatal complications.

We hypothesized that the standardized birth plan would facilitate communication between patients and health care providers and would result in high communication scores following delivery. Other objectives included an assessment of trust and satisfaction before and after delivery with use of the standardized birth plan. We also described the proportion of patients who stated they would use a birth plan with a subsequent delivery. By evaluating these factors, we sought to determine if the use of a standardized birth plan was associated with a positive birth experience. We estimated a pre-delivery satisfaction level of 6.0 (SD 2.5) and a post-delivery satisfaction level of 7.5 (SD 2.5) or higher. A sample of 40 patients would give us 80% power with a significance level of 0.05 using a paired t-test to be able to detect an increase of 1.5 in satisfaction score, which was deemed to represent a clinically meaningful increase.

Results

Eighty-one patients met inclusion criteria during the project period. The demographics of the study population are outlined in Table 2. Acknowledging the racial diversity of Hawai'i, where many people are multiracial, we allowed patients to indicate multiple races. The most commonly selected racial groups were Native Hawaiian/Pacific Islander (70%) and Asian (21%). The mean age of participants was 27.8 (SD 6.1) years. Though a wide range in education level was reported, almost half had a high school education or less (48%). Most patients had never used a birth plan prior to participating in the study (90%).
Most patients did not require cervical ripening prior to labor (93%) (Table 2). About three quarters of patients received an epidural in labor (78%) and had a spontaneous vaginal delivery (75%). Roughly half of all patients had artificial rupture of the membranes (51%) and were given oxytocin for labor induction or augmentation (51%). Antepartum complications were limited; few patients were diagnosed with intramniotic infection (5%)

and few neonates were admitted to the neonatal intensive care unit (1%). Postpartum complications were uncommon with few patients experiencing postpartum hemorrhage (6%) or retained their placenta requiring curettage (1%).

The majority of patients (84%) stated that they would use a birth plan if they were to deliver another baby. Mean communication, satisfaction, and trust scores before and after delivery are presented in Table 3. We found statistically significant increases in scores for satisfaction, communication, and trust after delivery though the increases were modest (increase of 1.4 for satisfaction score, 0.7 for communication, 0.5 for trust).

To determine whether certain demographic groups might benefit more from a standardized birth plan, we performed stratified analyses based on patient characteristics (parity, race, age, education). Increases in communication and trust scores were minimal for all groups while satisfaction scores increased more for parous women, women aged 26 to 35, and those with higher levels of education (Table 4, Table 5, Table 6).

Table 2. Demographics and Labor Characteristics of the Study Population

Characteristic	Number (%) N=81
Race*	
Native Hawaiian/Pacific Islander	57 (70)
Asian	17 (21)
White	16 (20)
Native American	1 (1)
Hispanic/Latina	4 (5)
Black	1 (1)
Declined to answer	1 (1)
Age	
25 years or less	34 (42)
26-35 years	36 (44)
36 years or more	11 (14)
Gravidity	
1	16 (20)
2-3	37 (46)
4 or more	10 (12)
No response	18 (22)
Parity	
0	18 (22)
1-2	39 (48)
3 or more	23 (28)
Education	
Grade school	3 (4)
Some high school	16 (20)
High school degree	20 (25)
Some college	24 (30)
College degree	15 (19)
Advanced degree	3 (4)
Previous use of a birth plan	
Yes	8 (10)
No	73 (90)
Type of Labor	
Spontaneous	20 (25)
Augmented	39 (48)
Induced	21 (26)
Unable to determine	1 (1)
Obstetric Procedures	
Cervical Ripening**	6 (7)
Use of oxytocin	41 (51)
Artificial rupture of membrane	41 (51)
Epidural	63 (79)
Type of Delivery	
Caesarean section	17 (21)
Spontaneous Vaginal Delivery	61 (75)
Forceps Assisted Vaginal Delivery	3 (4)

*Respondents could indicate more than one race so the same individual could be counted in more than 1 category. **Use of misoprotol, cervidil or foley balloon for cervical ripening

Table 3. Communication, Satisfaction, and Trust Scores Before and After Delivery (N=81)

	Before Delivery Mean (SD)	Range min, max	After Delivery Mean (SD)	Range min, max	*P*-value
Communication*	8.0 (2.2)	0.0, 10.0	8.7 (2.1)	0.2, 10.0	<.01
Satisfaction*	7.4 (2.3)	0.0, 10.0	8.8 (1.8)	0.6, 10.0	.02
Trust*	8.7 (2.0)	1.5, 10.0	9.2 (1.2)	5.0, 10.0	.04

* Compared using a paired t-test

Table 4. Stratified Analysis of Communication Scores Before and After Delivery

Characteristic	Before delivery Mean (SD)	After delivery Mean (SD)	*P*-value
Parity*			
Nulliparous (n=18)	7.6 (2.1)	8.5 (2.2)	.11
Parous (n=63)	8.2 (2.2)	8.7 (2.2)	.13
Race**			
Native Hawaiian (n=57)	8.3 (1.9)	8.7 (2.2)	.29
Asian (n=17)	8.1 (2.2)	9.2 (1.4)	.10
White (n=16)	8.4 (1.7)	7.9 (2.8)	.55
Education**			
High school or less (n=39)	8.1 (2.3)	8.7 (2.2)	.08
Some college (n=24)	8.3 (2.0)	8.5 (2.4)	.72
College degree (n=18)	7.7 (2.2)	8.7 (1.8)	.13
Age**			
25 years or less (n=34)	8.3 (2.5)	8.7 (2.3)	.34
26-35 years (n=36)	7.8 (2.0)	8.6 (2.2)	.10
36 years or more (n=11)	7.9 (1.7)	8.4 (1.3)	.36

* Compared using a paired t-test. **Compared using ANOVA.

Table 5. Stratified Analysis of Satisfaction Scores Before and After Delivery

Characteristic	Before delivery Mean (SD)	After delivery Mean (SD)	*P*-value
Parity*			
Nulliparous (n=18)	7.7 (1.8)	8.9 (1.7)	.06
Parous (n=63)	7.3 (2.5)	8.8 (1.9)	<.01
Race**			
Native Hawaiian (n=57)	7.3 (2.6)	8.8 (1.7)	<.01
Asian (n=17)	7.5 (1.9)	9.0 (2.3)	.08
White (n=16)	7.2 (1.5)	9.0 (1.7)	<.01
Education**			
High school or less (n=39)	7.5 (2.6)	8.6 (2.2)	.05
Some college (n=24)	7.3 (2.2)	9.1 (1.1)	<.01
College degree (n=18)	7.2 (1.9)	8.9 (1.6)	<.01
Age**			
25 years or less (n=34)	7.6 (2.4)	9.0 (1.6)	<.01
26-35 years (n=36)	7.1 (2.4)	8.7 (2.1)	<.01
36 years or more (n=11)	7.6 (1.9)	8.6 (1.3)	.04

* Compared using a paired t-test. **Compared using ANOVA.

Table 6. Stratified Analysis of Trust Scores Before and After Delivery

Characteristic	Before delivery Mean (SD)	After delivery Mean (SD)	*P*-value
Parity*			
Nulliparous (n=18)	8.3 (2.1)	9.2 (1.0)	.09
Parous (n=63)	8.7 (2.0)	9.2 (1.2)	.09
Race**			
Native Hawaiian (n=57)	8.8 (2.0)	9.2 (1.1)	.15
Asian (n=17)	8.8 (1.9)	9.4 (0.8)	.15
White (n=16)	8.8 (1.7)	9.0 (1.1)	.64
Education**			
High school or less (n=39)	9.1 (1.5)	9.4 (1.0)	.31
Some college (n=24)	8.3 (2.4)	8.8 (1.4)	.30
College degree (n=18)	8.2 (2.4)	9.3 (1.0)	.03
Age**			
25 years or less (n=34)	9.0 (1.8)	9.4 (1.0)	.21
26-35 years (n=36)	8.5 (2.2)	9.2 (1.0)	.03
36 years or more (n=11)	8.1 (1.8)	8.3 (1.7)	.80

* Compared using a paired t-test. **Compared using ANOVA.

Discussion

The birth plan was developed as a way for pregnant women to consider and prepare for the birth process. A birth plan can be a communication tool as it prompts discussion between women and their providers about desires, expectations, concerns, and misperceptions. Prior to this project, few women at the current clinic brought in a patient-initiated birth plan. We wanted to introduce the concept of a birth plan to our patients but thought it would be impractical to encourage each of them to find their own birth plan templates. We considered the introduction of a standardized birth plan to be a convenient way to discuss labor and delivery options that were available at our facility.

We conducted this quality improvement project in a group of racially diverse women. Women reported high communication (mean 8.7, SD 2.1), satisfaction (8.8, 1.8), and trust (9.2, 1.2) scores following delivery suggesting a positive birth experience. Though a comparison of scores before and after delivery revealed statistically significant increases, they were modest and may not have been clinically meaningful. Furthermore, the high pre-delivery scores make it difficult to show a meaningful increase. It is possible that patients who filled out their survey in the doctor's office could have felt pressured to provide a higher score than they would have had they responded at home, despite receiving reassurance that their answers to the surveys would not affect their medical care. Nonetheless, certain groups of women had higher increases in satisfaction scores following delivery while increases in communication and trust scores were minimal for most groups.

Birth plans can range in length and complexity. Many online birth plans are several pages in length, which can inhibit hospital staff from closely reviewing the document. Online birth plans may not address what is or is not available at a particular hospital, which may lead to unrealistic expectations on the part of the patient. Our birth plan was simple, two pages in length, took less than 10 minutes to complete, and included options that could be accommodated at our facility. Other than including an option for an epidural to manage pain, we purposefully did not include medical interventions such as the avoidance of artificial rupture of membranes or induction of labor. Online birth plans often discuss medical interventions and use phrases such as "unless absolutely or medically necessary." This creates disconnect between providers and patients as providers usually believe the recommendations they make are medically necessary even if they are not evidence-based.

Of note, we did not have a comparison group in this study. Though we can conclude that scores were high following delivery, we are unable to determine if satisfaction, trust, and communication would have been higher or lower if the standardized birth plan had not been used. We are also unable to determine if the increases noted in communication, satisfaction, and trust were due to implementation of the standardized birth plan. A feeling of satisfaction, especially, is more likely related to the delivery itself rather than use of a birth plan.

Despite these limitations, we provide a description of a standardized birth plan that was associated with a positive birth experience in terms of communication, trust, and satisfaction. Although we cannot conclude that the increase in communication, satisfaction, and trust scores were attributable to the birth plan, we found most patients (84%) reported they would use a birth plan with a subsequent delivery suggesting most patients found the birth plan to have a positive effect.

Conflict of Interest

None of the authors identity a conflict of interest.

Disclosure Statement

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MEDICAL SCHOOL HOTLINE

Advancing Suicide Prevention in Hawai‘i

Deborah Goebert DrPH and Jeanelle Sugimoto-Matsuda DrPH

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

Suicide is a serious, complex, preventable public health problem that can have lasting harmful effects on individuals, families, and communities. It is a leading cause of death in Hawai‘i, with more people dying from suicide than traffic-related injuries and drowning.[1] That is, about one suicide occurs every other day. Furthermore, in the last few decades, suicide death rates in the United States have significantly increased for nearly every age group, with the greatest increases among indigenous groups.[2] There has been an increasing trend in the number of people treated for nonfatal suicide attempts in emergency departments across the state.[1] Native Hawaiian and Pacific Islander adolescents exhibit the highest risk for suicide-related behaviors, especially those who reside in rural areas.[3]

Suicide prevention is a priority for the University of Hawai‘i, John A. Burns School of Medicine, Department of Psychiatry (JABSOM-DOP). For more than two decades, JABSOM-DOP has been a leader in suicide prevention efforts. JABSOM-DOP has been actively engaged in research and evaluation; education, training, and awareness; policy; and community and clinical service to reduce suicide deaths and attempts, and improve the well-being of the people of Hawai‘i.

JABSOM-DOP is home to Hawaii's Caring Communities Initiative for Youth Suicide Prevention (HCCI). With the goal of preventing youth suicide and increasing early intervention, projects positively impact communities that have higher rates, as well as the statewide suicide crisis infrastructure in Hawai‘i. JABSOM-DOP was well-positioned to obtain federal funding of our research and evaluation work cultivated by the National Center for Indigenous Hawaiian Behavioral Health. HCCI is having a ripple effect on communities throughout Hawai‘i as public awareness on suicide prevention is enhanced, more youth are identified and referred, and more youth, families, and communities are empowered to prevent future attempts.

Research and Evaluation

JABSOM-DOP conducts mixed-method, community-informed research and evaluation on suicide. Ultimately, our research and evaluation will help inform ways to improve program content and delivery to underserved populations and reduce health disparities related to suicide.

Indigenous Suicide

Since Hawai‘i began collecting suicide statistics in 1908, rates for Native Hawaiians have been increasing and are among the highest in the world for youth.[4-7] Youth Risk Behavior Survey (YRBS) studies from 1999-2009 show that Native Hawaiian and Pacific Islander adolescents self-reporting the highest rates of suicide-related behaviors (eg, depression, suicide ideation, suicide planning, suicide attempts, and suicide attempts requiring medical attention).[8] Furthermore, more Native Hawaiians from rural communities seek care in emergency rooms due to suicide attempts than other ethnic groups.[3] Comprehension of local and indigenous perspectives of suicide and well-being enhances our ability to develop better suicide prevention programs and services.[9-12]

Risk and Protective Factors

JABSOM-DOP research has identified talking with parents, higher levels of family cohesion, family organization, and parental bonding as family factors for preventing youth suicide attempts.[5] Families may also influence youth's choice of prosocial friends. A positive school climate increases social connectedness. Additionally, the community serves as a protective factor by enhancing the sense of connection and caring.[13] Risk factors associated with youth suicide in Hawai‘i include previous attempts, anxiety and depressive symptoms, alcohol and other substance use, high parental expectations, violence (cyberbullying, dating violence, victimization, perpetration), and historical trauma.[5,14-18]

Intervention Research

Through Hawaii's Caring Communities Initiative (HCCI) for Youth Suicide Prevention, youth and community members were trained as trainers to provide education and develop awareness projects and activities using evidence-based practices.[19] Our HCCI program was tailored to meet cultural needs that were identified by community leaders, which emphasized the importance of honoring community knowledge and prioritizing relationship.[20]

Education, Training, and Awareness

JABSOM-DOP has taken a leadership role in ensuring education and training needs are met in clinical and community settings. Physician education in suicide prevention has been shown to reduce suicide rates.[21-22] Furthermore, primary care physicians who feel competent in suicide prevention are more likely and willing to assess and treat suicidal patients in health care and community settings.[23-24] One of the goals of the National Strategy for Suicide Prevention is to increase the proportion of health care providers who receive training in the assessment and management of suicide risk.[25] The risk of suicide death can be significantly reduced (20%-70%) by training community-based health providers to recognize and respond to individuals feeling suicidal.[26] JABSOM-DOP has integrated suicide prevention into problem-based learning cases for medical trainees, serving as a leader in the country.[27-28] We also provide in-service training for health care providers.[29-30] Based on our experience, such training has sparked interest among participants in developing protocols and receiving additional training in asking about suicide, dealing with crisis situations, and lethal-means counseling.

Essential components of our provider trainings include recognizing the warning signs for suicide, evaluation, triage and crisis numbers, and protocol development. Local and national crisis numbers are:

Crisis Line Hawai'i
O'ahu: 832-3100; Neighbor Islands: 1-800-753-6879

Crisis TEXT Line: 741-741

National Suicide Prevention Lifeline
1-800-273-TALK (8255) Veterans Press 1

Military One Source
1-800-342-9647

Trevor Helpline
(LGBTQ Youth) 1-866-4-U-TREVOR (488-7386)

Hawai'i Poison Hotline
1-800-222-1222

JABSOM-DOP coordinates statewide suicide prevention training efforts. With a contract from the Hawai'i State Department of Health, Emergency Medical Services, and Injury Prevention System Branch, JABSOM-DOP provides and coordinates suicide prevention trainings statewide and maintains a trainer network. We have sponsored and supported evidence-informed suicide prevention trainings for trainers. We have master trainers for youth suicide prevention programs (*Connect Suicide Prevention Program* and Mental Health of America of Hawaii's *Ho'olohe Pono*-Listen Well, a youth suicide and bullying prevention curriculum) as well trainers in *SafeTalk*. JABSOM-DOP faculty and staff are active *Connect* trainers for community members, as well as, social service, emergency department, and mental health providers. JABSOM-DOP provides suicide prevention and postvention training to community members and Native Hawaiian and rural youth. Since 2011, JABSOM-DOP has trained over 700 community members and more than 500 youth annually.

JABSOM-DOP implements awareness activities in culturally relevant ways while using evidence-based practices of suicide prevention and safe messaging.[31-33] For example, our HCCI youth groups have partnered with cultural practitioners to hold workshops on hula, lei-making, basket-weaving, and fishing, to promote the strengths of the community. They have also conducted social media and radio campaigns, sign-waving, and shopping-mall presentations to provide a broad reach to all members of their community.

Policy

The Prevent Suicide Hawai'i Taskforce is a statewide partnership of organizations and community groups that provides leadership, develops strategies, coordinates activities, and monitors the progress of suicide prevention efforts in Hawai'i. JABSOM-DOP faculty have been involved since its inception, serving on the leadership committee, facilitating strategic planning, and developing and evaluating programs. Dr. Sugimoto-Matsuda currently chairs the Taskforce (2014, 2017-2018). On behalf of the Taskforce, JABSOM-DOP has coordinated two legislative briefings to highlight the magnitude of the problem, highlight gaps and community activities, and provide recommendations aligned with the State's strategic plan (2012, 2016). In 2016, the House Concurrent Resolution (HCR 66) was passed which calls for the Prevent Suicide Hawai'i Taskforce to develop a strategic plan to "reduce suicides in Hawai'i 25% by 2025." The legislation named JABSOM-DOP as a member of the group tasked with facilitating this process and developing the plan. The report to the legislature is due December 2017. For the current strategic plan, see the Hawai'i Department of Health's website.[34] The new plan will be posted on this site, once it is released.

The Youth Leadership Council for Suicide Prevention was formed to provide a youth voice for statewide suicide prevention work, leadership development and training on suicide prevention, and civic engagement and community service opportunities. Youth leaders are connected with adults who support them as leaders in their home communities. Convened and coordinated by Mental Health American of Hawai'i, JABSOM-DOP serves on the leadership team as a planner and supportive adult. JABSOM-DOP has created a toolkit of activities for members to use to promote suicide prevention in their communities.[35]

On a national level, faculty have served as contributors to the Suicide Prevention Resource Center (SPRC) and the National Action Alliance for Suicide Prevention relating to minorities, emergency departments, and community.[36-38]

Service

JABSOM-DOP is the largest provider of psychiatric services in Hawai'i. Ensuring that effective, quality care for suicide risk is available is a fundamental component of our clinical services. It requires a systems approach that integrates community and

health care services. A systems approach focuses on the interconnections among individuals, their families, providers, and organizations, and can improve health by considering the various elements involved in caring for each community member and the multiple factors influencing health. JABSOM-DOP has promoted local adoption of the Zero Suicide Conceptual Approach and Practice, a system-wide approach that aspires to improve care and outcomes for individuals at risk for suicide in health care systems.[39]

For suicide prevention efforts to be effective, providers and community members need to identify accurately those at risk. Most individuals (83%) have had health system contact in the year before suicide; however, few of them have a documented mental health diagnosis.[40] Suicide screening and assessment are often conducted by behavioral health teams. JABSOM-DOP provides psychiatric services as part of these teams. Medical centers have initiated screening and evaluation of patients for suicidal ideation, improving recognition and treatment. While an increasing number of Hawaii's hospitals provide routine screening for suicide risk, only 20% of hospitals have access to on-site psychiatric consultation, such our primary training sites at The Queen's Medical Center and Kapi'olani Medical Center.

The Queen's Medical Center's Family Treatment Center, an adolescent psychiatric inpatient unit, promotes the health and well-being of Hawaii's adolescents and their families by providing inpatient mental health services for youth of whom, the vast majority suffer suicidality. The *Cultural Integration Program* considers values that are essential for well-being. Developing prosocial cultural values can provide adolescents with a foundational guide for beliefs, social behavior, and attitudes that can lead to honest, socially acceptable, and responsible decisions.[41] The goals of this program at The Queen's Medical Center, Family Treatment Center are to reinforce specific values in therapy as well as in the treatment milieu. Most recently, the unit began a collaborative project on healing through art, in which murals along its walls reflect Native Hawaiian cultural values.[42]

There are many empirically supported medication and non-medication treatments for mental health illnesses, including depression, bipolar disorder, and anxiety that have potential for suicide prevention.[43-45] For example, cognitive behavioral therapy (CBT) has been adopted for suicide attempters, demonstrating significantly lower reattempt rates for those receiving CBT compared to the usual care group. Other related approaches, including dialectical behavior therapy, problem-solving therapy, developmental group therapy, and psychoanalytic approaches have also been shown to reduce suicidality. Brief behavioral interventions provide knowledge about suicidal behaviors and constructive coping strategies regarding treatment and referral, demonstrating a reduction in suicide risk when delivered by staff in primary care clinics and emergency departments targeting treatment and non-treatment seekers.[46-47] Large studies on pharmacotherapy, particularly selective serotonin reuptake inhibitors (SSRIs), have shown that initiation is not associated with increased risk and continuation is related to decrease risk.[44] Ketamine may be an effective and rapid treatment of suicidal thoughts with minimal side-effects.[45] Our work has shown promise for reducing suicidality among geriatric patients using Ketamine.[48] Electroconvulsive therapy has also demonstrated a rapid reduction in suicide risk.[49] It is important that providers actively engage not only the person considering suicide, but also the care system, family, and community supports, when providing direct suicide intervention services, particularly for minority and indigenous populations.

Suicide has a devastating impact on families, friends, and communities. Postvention refers to activities to reduce risk and promote healing after a suicide death. JABSOM-DOP is working to increase the capacity of communities to respond effectively to suicide clusters and contagion within their cultural context, and support postvention implementation with education, training, and consultation. In response to community requests, JABSOM-DOP has mobilized a Suicide Postvention Response Team to promote healing and impart hope to survivors of suicide loss. Although postvention is implemented after a suicide, it is essential that communities and organizations prepare for postvention before a suicide, usually through training and provision of resources.[50]

JABSOM-DOP is recognized for its ongoing efforts as leaders in formulating and implementing suicide prevention initiatives in Hawai'i. However, this work is too big and too important to be accomplished by one department. JABSOM-DOP continues to partner to create suicide-safer communities across the Hawaiian Islands though innovative research and programs and evidence-informed education, policy, and service.

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Ambulatory Blood Pressure Monitoring: Underuse in Clinical Practice in Hawai‘i

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Abstract

Hypertension is one of the leading causes of death and disability worldwide. Blood pressure reduction and control are associated with reduced risk of stroke and cardiovascular disease. To achieve optimal reduction and control, reliable and valid methods for blood pressure measurement are needed. Office based measurements can result in 'white coat' hypertension, which is when a patient's blood pressure in a clinical setting is higher than in other settings, or 'masked' hypertension, which occurs when a patient's blood pressure is normal in a clinical setting, but elevated outside the clinical setting. In 2015, the US Preventative Services Task Force recommended Ambulatory Blood Pressure Monitoring (ABPM) as the "best method" for measuring blood pressure, endorsing its use both for confirming the diagnosis of hypertension and for excluding 'white coat' hypertension. ABPM is a safe, painless and non-invasive test wherein patients wear a small digital blood pressure machine attached to a belt around their body and connected to a cuff around their upper arm that enables multiple automated blood pressure measurements at designated intervals (typically every 15 to 30 minutes) throughout the day and night for a specified period (eg, 24 hours). Patients can go about their typical daily activities wearing the device as much as possible, except when they are bathing, showering, or engaging in heavy exercise. Given the importance of blood pressure monitoring and control to population public health, this article provides details on the relevance and challenges of blood pressure measurement broadly then describes ABPM generally and specifically in the Hawai‘i context.

Cardiovascular disease is the leading cause of death in the United States. Annual cardiovascular disease costs exceed $316 billion.[1] Coronary heart disease, the most common type of cardiovascular disease, results in 365,000 deaths annually.[1] Stroke, another form of cardiovascular disease, is the 5th leading cause of death in the United States, also results in serious, long-term disability.[2,3]

These are important issues in Hawai‘i. Heart disease is the leading cause of death, responsible for at least three out of every ten deaths in the state.[4] Stroke is the 3rd leading cause of death in Hawai‘i.[2,3] Considerable racial/ethnic disparities in cardiovascular disease and stroke also exist in Hawai‘i. Compared to other races/ethnicities in Hawai‘i, Native Hawaiian and Filipino men have the highest cardiovascular disease mortality at 160 and 153 per 100,000 population for Native Hawaiian and Filipino men, respectively. This rate is far higher than the cardiovascular disease mortality of 100 per 100,000 population among white men and the Healthy People 2020 goal.[4] For women, coronary heart disease mortality is also highest for Native Hawaiians and Filipinos. Filipino men and women had the highest stroke mortality, at almost twice that of other races/ethnicities.[4]

Addressing cardiovascular disease risk is critical to improving population health and reducing health care costs. A number of lifestyle modifications and pharmacological treatment of risk factors can reduce these risks. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for cardiovascular disease prevention are highly complex and address multiple factors including hypertension, dyslipidemia, diabetes, lifestyle risk factors, and medication use.[5]

Of all of these, a focus on managing hypertension would be particularly fruitful for reducing morbidity and mortality. Hypertension is the leading cause of death and disability worldwide, reflecting the shift in the causes of global disease burden from communicable diseases in children to non-communicable diseases in adults.[6] Hypertension is also the leading cause of coronary heart disease and stroke. The impact of high blood pressure on stroke is ten times more than any other risk factor.[7] Predictive modeling suggests a 10% increase in treatment of hypertension could prevent 14,000 premature deaths each year.[8] A recent systematic review showed that adequate antihypertensive treatment as a secondary stroke prevention significantly lowered the risk of recurrent stroke, disabling or fatal stroke, and cardiovascular death. These benefits were linearly associated with the extent of both systolic and diastolic blood pressure reduction.[9] Moreover, a modest reduction of diastolic blood pressure by only 5 mm Hg is estimated to reduce the incidence of stroke by 32% and ischemic heart disease by 20%.[10]

In 2015, 32% of adults in Hawai‘i had been told by a doctor that they had hypertension, and this prevalence is increasing.[11] Given the importance of blood pressure monitoring and control to population public health, this article provides details on the relevance and challenges of blood pressure measurement. We also describe the utility of ABPM generally and specifically in the Hawai‘i context.

Guideline Recommendations on Screening

The US Preventative Services Task Force (USPSTF) recommends annual screening for adults aged 40 years and older, and for those with risk factors for hypertension, including those with high-normal blood pressure, those who are overweight or obese, and African Americans. Adults aged 18 to 39 years with normal blood pressure and without other risk factors should be rescreened every 3-5 years. Such screening typically takes place in a doctor's office.

Office Blood Pressure Measurement

In a health care provider's office, blood pressure is most commonly measured with a manual or automated sphygmomanometer. Although there is no consensus on the best method to measure blood pressure, many hypertension clinical trials averaged at least 2 measurements, taken when the patient was seated, after 5 minutes of sitting, and using an appropriately sized cuff with the patient's arm relaxed and the cuff at the level of heart during measurement. However, because blood pressure is affected by short-term factors, such as stress, pain, physical activity, caffeine and other drugs, there are concerns that office-based measurement of blood pressure may be inaccurate. Additionally, there may be measurement errors due to the use of a cuff that is inappropriately sized for that patient or too few measurements due to time pressures, which can also increase the risk of clinic-based hypertension results.

'White coat' hypertension, which affects approximately 36% of patients, occurs when a patient's blood pressure in a clinical setting is higher than in other settings.[12-14] Because patients may be falsely diagnosed with hypertension, 'white coat' hypertension can lead to overtreatment. In contrast, 'masked' hypertension occurs when a patient's blood pressure is normal in a clinical setting but elevated outside of a clinical setting. 'Masked' hypertension is estimated to be present in 17% of patients and can occur if the doctor's office is less stressful than home or other settings or if patients engage in health-related behaviors at home, such as drinking or smoking, which may increase their blood pressure. Although less common than 'white coat hypertension', 'masked' hypertension also puts patients at increased risk as it can lead to undertreatment.[15-17]

Home Blood Pressure Monitoring

Besides office blood pressure measurement, home based blood pressure methods may be used to confirm a diagnosis of hypertension after initial screening. Home blood pressure measurement devices have become increasingly affordable and common, with many having undergone technical validation according to recommended protocols. These are also commonly used by patients with known high blood pressure. Despite its prevalence, the accuracy of home-based blood pressure measurements can be inconsistent, particularly in the absence of a standardized protocol, and comparisons to office blood pressure measurements is surprisingly sparse.

Ambulatory Blood Pressure Monitoring

In 2015, the USPSTF recommended Ambulatory Blood Pressure Monitoring (ABPM) as the "best method" for measuring blood pressure and endorsed its use for confirming the diagnosis of hypertension and excluding white coat hypertension (described below).[10] In 2011 in the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommended that ABPM be performed on all patients with suspected hypertension to confirm the diagnosis and reduce unnecessary treatment in people who do not have true hypertension.[18]

ABPM is a safe, painless and non-invasive test that enables multiple automated blood pressure measurements at designated intervals (typically every 15 to 30 minutes) throughout the day and night for a specified period (eg, 24 hours). Patients wear a small digital blood pressure machine that is attached to a belt around their body and connected to a cuff around their upper arm. The device will beep and then the cuff will inflate and take the patient's blood pressure. Patients are asked to go about their typical daily activities wearing the device as much as possible, except when they are bathing, showering, or engaging in heavy exercise. Guideline ABPM blood pressure goals are lower than office-based (less than 140/90): the American Heart Association suggests an ABPM 24-hour blood pressure average of less than 130/80.[19]

ABPM has been found to reflect more accurately a patient's blood pressure and to better predict cardiovascular risk than office-based blood pressure measurement.[20-22] ABPM is also able to identify 'white coat' and 'masked' hypertension. ABPM also provides other information that can help the health care provider. First, ABPM can track a patient's blood pressure response after taking medication. It also measures other conditions including: non-dipping blood pressure (ie, when a patient's blood pressure does not decrease as expected at night), nocturnal hypertension, larger than expected morning surge, blood pressure variability, and hypotension.[23] Patients experiencing any of these conditions may be difficult to identify using typical office-based or even home-based blood pressure monitoring, and information from ABPM may lead to appropriate changes in their medication treatment regimen.

Barriers to ABPM Utilization

Despite the advantages of ABPM and its recommended use by the USPSTF, ABPM is markedly underutilized in clinical practice.[20-22,24] Barriers to ABPM include its expense, as health care providers or offices must purchase at least one unit to have and loan to patients (approximately between $1500 and $3000 per unit depending on the device and software). Unfortunately, ABPM is not commonly reimbursed for conditions other than 'white coat' hypertension and, when reimbursed, payment is low. Even for 'white coat' hypertension, there are barriers in terms of strict conditions and documentation. According to the National Coverage Decision by the Centers for Medicare & Medicaid Services (CMS), for Medicare to cover ABPM,

providers need to document suspected 'white coat' hypertension with the following: (1) Office blood pressure >140/90 mm Hg on at least three separate clinic/office visits with two separate measurements made at each visit; (2) At least two documented blood pressure measurements taken outside the office which are <140/90 mm Hg; (3) No evidence of end-organ damage.[25-27]

ABPM may also be burdensome to patients in that they need to wear the device for at least 24 hours. Some patients report that having the device activate at night affects their sleep patterns.[28] Additionally, physicians are generally unaware or unfamiliar with ABPM, and there is a lack of certification and training in ABPM implementation and interpretation, including in Hawai'i.[28] A recent internal quality improvement survey of 33 cardiologists and internists administered at a clinicians' conference at Queens Medical Center found only 3% of cardiologists and internists had used ABPM, with 30% reporting no knowledge, 70% some knowledge, and no one reported 'extreme' knowledge. Encouragingly, 61% reported being 'extremely interested' in learning more about ABPM, 39% were 'somewhat interested', and no one was 'not interested.'

Potential Impact of Payment Transformation

Payment transformation may encourage the use of ABPM. The cost of an ABPM device may be prohibitive for a single primary care provider particularly under fee-for-service systems as the reimbursement is so low; however, public and private insurer movement toward bundled payments may encourage use of ABPM. In Hawai'i, the largest insurer has moved away from fee-for-service payment toward bundled payments and global reimbursement with performance bonuses for Primary Care Providers (PCP).[29] This incentivizes coordination between inpatient and outpatient care, a focus on outcomes (including blood pressure control), and health care system support of PCP. Under an Accountable Care Organization (ACO) or similar arrangement, purchasing an ABPM device may be more cost-effective because it can be used across a larger patient population than that of a single practitioner. Moreover, it may be seen as a means of achieving improved blood pressure control that may be an incentivized outcome measure for health care quality with bonus payment. There may also be shared savings involved if reductions can be made in overtreatment of patients with 'white coat' hypertension as well as with improved treatment of patients with 'masked' hypertension.

Conclusion

Despite evidence that ABPM is more accurate than office-based blood pressure measurement and more likely to predict adverse cardiovascular outcomes, ABPM is underused in clinical practice generally and specifically in Hawai'i. However, greater use may bring important health improvements on an individual patient level as well as a population level, especially to reduce health disparities given the higher rates of risk in some communities. Barriers to access, including lack of education and training, need to be addressed. Awareness in Hawai'i is low. Cost is another barrier that may be addressed as payment transformation focused on bundled payments, incentives for improved clinical quality, and shared shavings may encourage use of ABPM by health care organizations. A greater emphasis on team-based care might also increase use of ABPM, as pharmacists and other allied providers might be able to educate patients on ABPM and facilitate its use. Future research is needed to assess whether routine utilization of ABPM increases the likelihood of high-risk patients, particularly in groups with known health disparities, to achieve guideline-based target blood pressure goals.

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Targeted Nanocarrier Based Systems for the Treatment of Lung Cancer

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Abstract

In Hawai'i, lung cancer is among the top cancers diagnosed and a leading cause of death. Despite current understanding and modern surgery, radiology, and chemotherapy techniques, the survival of those suffering from lung cancer remains low. Current anticancer drugs have poor tumor tissue selectivity and toxicity issues that contribute to their overall low efficacy, detrimental effects to normal tissues, and drug resistance. A potential way of mitigating cancer is through RNA interference (RNAi) by the delivery of small interfering RNA (siRNA) to target select proteins or genes involved in cancer progression, known as oncoproteins or oncogenes, respectively. However, the clinical utility of delivering unformulated siRNA has been hindered due to poor cell penetration, nonspecific effects, rapid degradation, and short half-life. As an alternate for conventional chemotherapy, nanoparticles (AKA nanocarriers) may be designed to localize within the tumor environment and increase targeted cell internalization, thus reducing systemic adverse effects and increasing efficacy. Nanoparticles play important roles in drug delivery and have been widely studied for cancer therapy and diagnostics, termed collectively as theranostics. Nanoparticles composed of natural and artificial polymers, proteins, lipids, metals, and carbon-based materials have been developed for the delivery of siRNA. Cancer targeting has been improved by nanoparticle surface modification or conjugation with biomolecules that are attracted to or stimulate therapeutic agent release within cancer tissues or cells. In this mini-review article, we present recent progress in nanocarrier-mediated siRNA delivery systems that include lipid, polymer, metallic and carbon-based nanoparticles for lung cancer therapy.

Introduction

Cancer is a leading cause of death in Hawai'i and is characterized as a set of diseases that involve abnormal cell growth that may initiate in one location and then metastasize, or invade other tissues in the body.[1] Despite the recent advances in diagnosis and treatment, lung cancer is among the most common cancers diagnosed on the islands only following prostate and breast cancers in both men and women, respectively.[1,2] The Native Hawaiian and Pacific Islander populations that originate from Hawai'i, Guam, Samoa, or other Pacific islands are among the fastest-growing populations in the United States (U.S.) and have increased cancer rates than Asian Americans.[3] Due to different rates of smoking habits, lung cancer rates in Samoan men are about 30% higher than those in Native Hawaiian men.[3] Worldwide, in 2016 there were approximately 58,000 new cancer cases and nearly 17,000 cancer deaths among Asian Americans, Native Hawaiians, and Pacific Islanders.[3] In Hawai'i, about 6,500 Hawai'i residents are diagnosed with invasive cancer and more than 2,000 die from the disease each year.[4]

Overall nationally, an estimated 221,200 lung cancer cases were detected and diagnosed in 2015 that made up approximately 13% of all cancer diagnoses.[5] The lung cancer 5-year survival rate is 54% when the disease is still localized within the lungs, however only 15% of cases are diagnosed at early stages.[6] For metastasized tumors, the 5-year survival rate is 4%.[6] The overall lung cancer survival rate is much lower than other leading cancer causes.[6] Non-small cell lung cancer (NSCLC) occurs when malignant cells form in the tissues of the lung and can be classified as adenocarcinoma, carcinoid tumor, large cell carcinoma, pleomorphic, salivary gland carcinoma, squamous cell carcinoma, and unclassified carcinoma.[2] NSCLC accounts for 85% of the total cases of lung cancer, where 75% of these cases at diagnosis are metastatic.[7] Small-cell carcinoma, also known as oat-cell carcinoma, is an aggressive cancer that begins in the bronchi and rapidly spreads, or metastasizes, throughout the body. Small-cell carcinoma occurs most often in smokers, almost exclusively, and represents approximately 15% of lung cancers in the U.S.[8,9]

Standard lung cancer treatment entails combinations of surgery, chemotherapy, and radiation therapy. Although early detection and treatment make a significant difference in life expectancy, many lung cancer patients are diagnosed with the advanced or metastatic disease.[10] Surgical resection may be considered the most effective strategy to cure NSCLC; however, surgery is not possible in every case.[11] Current NSCLC anticancer drugs have poor tumor tissue selectivity and toxicity issues that contribute to their overall low efficacy and detrimental effects to normal tissues.[12] Chemotherapy options often have issues with multidrug resistance due to overexpression of drug-resistance genes that drive mechanisms to stop cancer cell death and increase the expression of cellular pumps that remove the anti-cancer drugs from the cells. Multidrug resistance leads to higher chemotherapy doses that in turn, lead to more risk for severe adverse effects. New treatment options for lung cancer include the drugs afatinib (Gilotrif), ramucirumab

(Cyramza), and bevacizumab (Avastin).[13] Afatinib, approved by the U.S. Food and Drug Administration (FDA) in 2013, targets the epidermal growth factor receptor (EGFR) and receptor tyrosine-protein kinase erbB-2, AKA Her2/neu, via irreversible covalent inhibition to inhibit metastasis and tumor growth in EGFR mutant positive NCSLC patients.[14-16] Mutations in the expression or activity of receptor tyrosine kinases EGFR and ErbB-2 causes cancer.[17] Ramucirumab, FDA approved in 2014, is a monoclonal antibody that acts as an angiogenesis inhibitor by binding the vascular endothelial growth factor 2 (VEGFR2).[18] However, conventional delivery of these therapies leads to the potential intolerable side effects and risk of recurrence due to resistance.

More effective pharmacological interventions for cancer therapy are necessary because surgery and radiotherapy are not viable options in some patients and chemotherapy results in low response rates with detrimental adverse effects. A well-designed delivery system that can deliver anticancer therapeutics specifically to cancerous cells should be developed to avoid adverse effects and to increase efficacy.

Cancer Targeting siRNA Therapeutics

Several methods have been proposed to control protein markers that are overexpressed in cancer.[19] These methods include small molecule inhibitors or antibody biologics. A method for downregulating protein expression that targets the mRNA level, before protein transcription even begins, is RNA interference (RNAi). RNAi is a naturally occurring protein regulating process that has a high degree of specificity and the potential to silence mRNA and associated protein expression.[20] A method for eliciting RNAi is mediated through the delivery of small-interfering RNAs (siRNAs) to the cell cytoplasm of target cells. Therapeutic siRNAs are synthetic double-stranded RNA of 21-23 base pairs that can be designed to suppress target mRNA sequences, in a process known as post-transcriptional gene silencing. To exert the therapeutic effect, the siRNA must travel to the cell cytoplasm to be attached to the multi-protein RNA-induced silencing complex (RISC).[21] Intracellular siRNA, specifically targeted to a particular mRNA for degradation, undergoes RNAi processing in the cell to induce short-term silencing of protein coding mRNA.[22] The siRNAs, as a class of therapeutic agents, are capable of efficient knockdown of targeted oncoproteins and oncogenes, as well as those proteins that play a role in multidrug resistance, and therefore have great potential for the treatment of lung cancer or other diseases.[23]

Nanotechnology in Drug Delivery

Nanotechnology has greatly impacted the field of medicine which in part has catapulted preclinical siRNA delivery systems into a new era. Drug half-life, retention, and targeting efficiency can be increased along with a subsequent reduction in adverse effects by incorporating nanotechnology-based therapeutic delivery systems. A brief history of the breakthroughs in cancer nanomedicine, or the therapeutic application of nanoparticle drug delivery systems, is shown in Figure 1.[24] A few chemotherapeutic nanoparticle formulations have been approved by the FDA, namely liposomal doxorubicin (Doxil) and Nab-paclitaxel (Abraxane).[25-29] Bind Biosciences, Inc. demonstrated nanoparticles containing a combination of chemotherapeutic and prostate-specific membrane antigens (PSMA) that outperform either drug alone at diminishing lesions of the lung and tonsillar regions and that the formulation greatly lowered the required dose.[30,31] Calando Pharmaceuticals established the foremost clinical evidence of RNAi using a polymeric nanoparticle delivery system known as CALAA-01.[32,33]

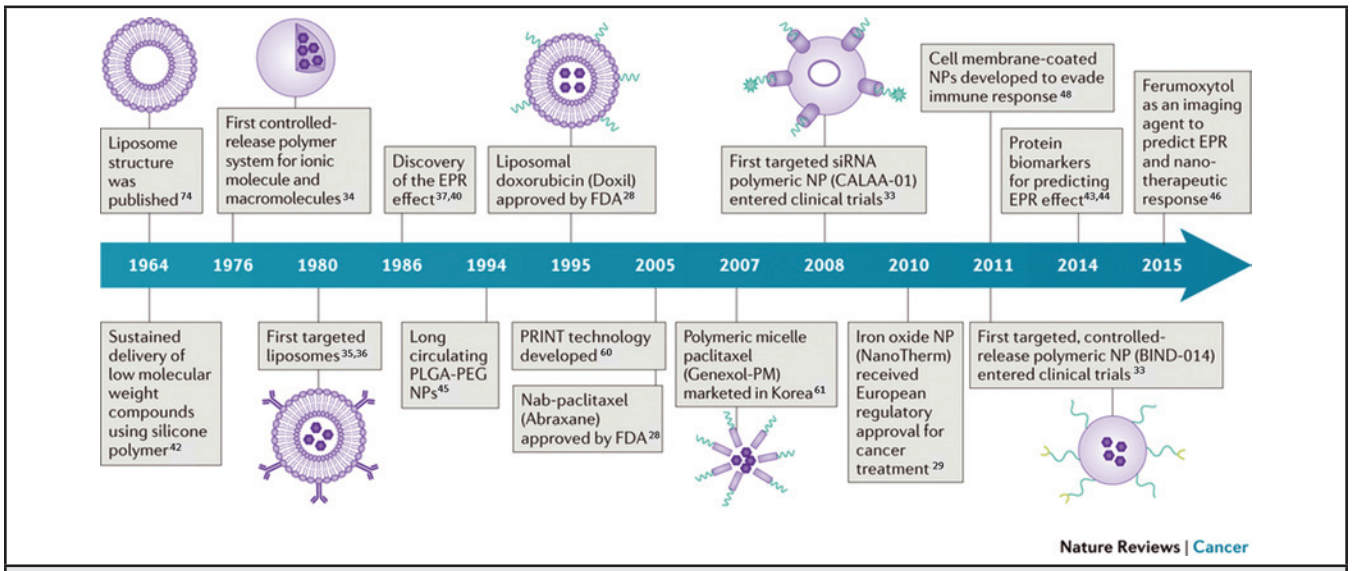

Figure 1. A timeline showing the history of major cancer nanomedicine breakthroughs.
Figure adapted with permission from Nature Publishing Group: Nature Reviews Cancer, 2017.[24]

As opposed to conventional chemotherapy delivery where the drug is administered systemically by i.v. injection and shows various drug concentrations in all tissues of the body, lung cancer targeting strategies using nanocarriers may achieve controlled release and are classified as having either passive or active targeting directly to cancer tissue.[34-36] Passive cancer targeting is possible through the enhanced permeation and retention (EPR) effect that has been exploited in many cancer drug delivery systems since its identification in the late 1980's.[37-40] Nanocarrier circulation times and accumulation levels in tumor tissues are influenced by the properties and characteristics of the nanocarriers, such as the polymer or lipid, surface molecules, particle size, or surface charge.[41-46]

Strategies to improve delivery to tumor sites by including microenvironment homing mechanisms including tumor penetrating peptide and stimuli responsive functional surface nanocarrier modifications have been explored.[47] In addition to conjugating the polymer polyethylene glycol (PEG) to the surface of the nanoparticles, known as PEGylation, cell membrane-coated nanoparticles have been developed to evade immune responses by tricking the immune system.[48] Active targeting involves molecular targeting agents, such as surface bound ligands, to specifically target the biomarkers or receptors on cancer tissues or cells that may provoke uptake of nanocarriers.[49-51]

Nanocarrier-based siRNA Delivery Systems for Lung Cancer

Naked siRNA is prone to degradation, has a shorter plasma half-life, rapid renal clearance, and limited permeability across cell membranes, making clinical efficacy unlikely.[52,53] A variety of nanocarrier systems in early cancer therapeutic clinical studies have shown enhanced efficacy and reduced side effects.[30,54] Cationic lipid based systems have emerged as the most attractive for siRNA delivery. However the use is limited due to poor transfection efficiency and toxicity *in vivo*.[55] Natural polymer based delivery systems are biocompatible and biodegradable with high physiological tolerance and low immunogenicity.[56,57] Rigid nanoparticles are composed of inorganic metals or of carbon-based materials.[58] Here, we focus on siRNA nanocarriers that have undergone laboratory experimentation published recently.

Examples of Polymer-based siRNA Nanocarriers

Polymers used for siRNA nanocarriers include naturally occurring ones, such as chitosan, or synthetics ones, such as polyethylenimine (PEI). Polymeric nanocarriers have received much attention in the area of siRNA delivery because of their biocompatibility and versatile modifiability.[32,54,59-61]

Yan, et al, developed a combinatorial functional polyester library to identify formulations that have highly efficient delivery of siRNA to A549 (ATCC® CCL-185™) human epithelial lung carcinoma for potential lung delivery of siRNA.[62] They found that two types of polyplex nanoparticles that contained PEG 2000 DMG modified lipid or Pluronic F-127 nonionic surfactant on their surface increased their serum stability and decreased their surface charge. This study showed that inhalation of the surface modified polyplex nanoparticles had resulted in significantly more nanoparticles localized within the lungs and significant gene downregulation in the A549 orthotropic lung tumors than when delivered by i.v. administration.

Another study that evaluated nanocarriers in an A549 lung cancer cell line was conducted by Seifi-Najmi, et al, who demonstrated the preparation and characterization of varying combinations of doxorubicin, High Mobility Group At-Hook 2 (HMGA2) siRNA, or combination siRNA/doxorubicin entrapped within carboxymethyl dextran trimethyl chitosan nanocarriers.[63] Nanoparticles loaded with doxorubicin combined with HMGA2 siRNA outperformed the other formulations in treated A549 cell assays including lessened cancer cell viability, alteration of pro-cancer markers, induction of apoptosis, and inhibition of migration.

Cisplatin is an anti-cancer chemotherapy drug, also known as a cytotoxic or antineoplastic drug, that interferes with DNA replication by crosslinking DNA, thus preventing cell division by mitosis. However, cellular resistance to cisplatin therapy is commonly observed. A mediator of cisplatin sensitivity in human cancer cells at the mitotic checkpoint is the mitotic arrest deficient-2 (Mad2) protein.[64] Nascimento, et al, designed chitosan polysaccharide (sugar polymer) nanoparticles containing surface conjugated EGFR targeting ligand that entrapped Mad2 siRNA in combination with cisplatin and determined them to be safe and efficacious in cisplatin resistance and sensitive NSCLC cell culture models.[65,66] Their rationale was if the RNAi that downregulated the essential mitotic checkpoint gene Mad2, the cells would become more sensitive to cisplatin based chemotherapeutics and therefore lead to increased cellular death. EGFR targeted nanoparticles presented a steady and favored tumor targeting capability with fast blood plasma clearance to penetrate and localize within the tumor tissue for up to 4 days.[67] These targeted nanoparticles showed a six-fold advanced tumor targeting ability when related to non-targeted chitosan nanoparticles.[67]

Another siRNA and chemotherapeutic combination study was conducted by Xu, et al, who designed a pH-responsive PEI nanoparticle containing doxorubicin and Survivin siRNA for potential inhalation therapies for metastatic lung cancers.[68] Survivin is a protein that inhibits caspase activation, which causes negative regulation of programmed cell death, or apoptosis; thus it belongs to the family of proteins that inhibit apoptosis.[69] Therefore, siRNA directed towards survivin expression will remove this negative regulation, allowing for normal cell death of cancerous cells. Doxorubicin release from these PEI nanocarriers was pH dependent, where the release was higher in acidic tumor microenvironments. The doxorubicin and Survivin siRNA was delivered in vitro and was shown to impart cellular death in B16F10 cancer cell culture lines. Using cancer mouse models that had B16F10 tumors, locally delivered siRNA loaded doxorubicin coupled PEI nanoparticles by inhalation resulted in the accumulation of doxorubicin and Survivin siRNA within the lung tissue and airways, where a

substantial quantity of doxorubicin and siRNA were found in tumor tissues, with a low amount of doxorubicin and siRNA observed within normal lung tissues. Furthermore, the Survivin siRNA doxorubicin conjugated PEI nanoparticles presented superior antitumor effectiveness when compared to individual doxorubicin or Survivin siRNA delivery.

Srikar, et al, produced tri-block nanoparticles that were composed of enzymatically degradable gelatin nanoparticles with cetuximab-siRNA molecules conjugated to its surface and entrapped with the tyrosine kinase inhibitor, gefitinib.[70] Delivery of siRNA to chemotherapeutic resistant KRAS mutated NSCLC cells via a targeted strategy was believed to foster cell sensitization to tyrosine kinase inhibitors, leading to increased cellular death. This study demonstrated targeted proto-oncogenes with nanoparticle therapies.

Metformin is a well-known diabetic medication that has been studied as an anti-cancer drug. Its mechanism is believed to rely on the ability to reduce insulin resistance and indirectly lower levels of insulin, a known cancer cell growth promoter, as well as through direct inhibition of cancer cell growth.[71] Zhao, et al, prepared a polymer conjugate of Metformin, coined PolyMetformin through dicyandiamide conjugation to linear PEI.[72] The positive charge of PolyMetformin facilitated the entrapment of the negatively charged siRNA into a core-membrane structured lipid-polycation-hyaluronic acid nanoparticle as shown in Figure 2. Vascular endothelial growth factor (VEGF) is a signaling protein that stimulates blood vessel formation, and if expressed by cancer cells can cause tumor growth and metastasis.[73] LPH-PolyMetformin nanoparticles facilitated VEGF siRNA delivery in a human lung cancer xenograft, leading to hindrance of tumor tissue growth. Without RNAi, the lipid-polycation-hyaluronic acid-PolyMetformin nanoparticles were able to induce antitumor efficacy similarly to Metformin. PolyMetformin was combined with siRNA to further improve the therapeutic activity of an anti-oncogene and oncoprotein therapy.

Examples of Lipid-based siRNA Nanocarriers

Several siRNA loaded lipid nanoparticle delivery systems have undergone evaluation as cancer therapies within clinical trials. However none have specifically targeted lung cancer. Lipid-based siRNA nanocarriers include liposomes, lipid complexes, and solid lipid nanoparticles.[74] Phase I clinical trials of stable nucleic acid lipid particles (SNALP) encompassing siRNA's directed towards serine/threonine-protein kinase (PLK1), a mitosis regulating gene, for cancer therapy was initiated by Tekmira Pharmaceuticals Corporation (NCT01262235, BC, Canada).[75,76] The Anderson Cancer Center (Texas, USA) initiated a Phase I clinical trial where siRNAs encapsulated within a neutral liposome composed of 1,2-dioleoyl-sn-glycero-3-phosphatydylcholine for oncoprotein Eph2 suppression (NCT01591356) for delivery for the treatment of advanced cancers.

Lung cancer and mesothelioma tumorigenesis, or the onset of tumor growth, has been associated with the receptor EphA2 overexpression. A liposomal cisplatin formulation, known as Lipoplatin™ , has been administered against cisplatin resistant cancers. To further enhance the sensitivity of lung cancer cells to Lipoplatin, Lee, et al, combined receptor EphA2 siRNA with Lipoplatin and targeted them to tumor cells.[77] This group demonstrated that silencing EphA2 significantly enhanced the cellular sensitivity of lung tumor and malignant pleural mesothelioma cells to Lipoplatin.[77]

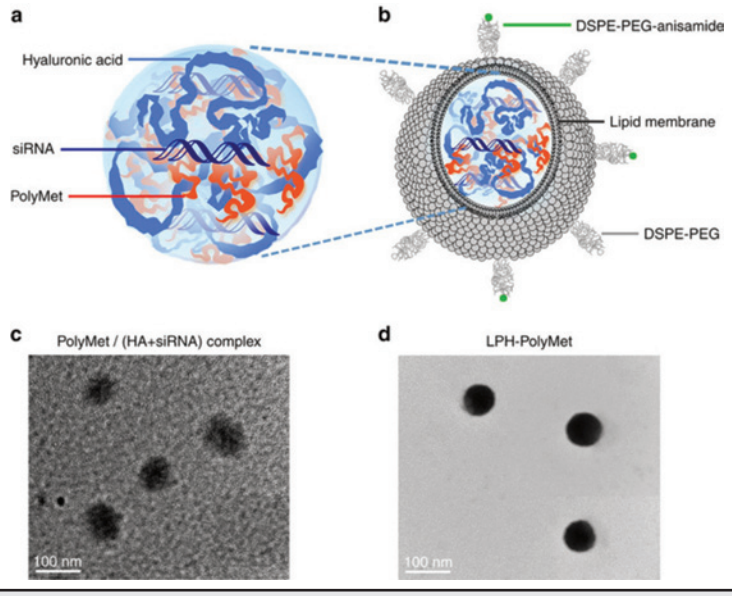

Figure 2. Schematic illustration and representative TEM images of PolyMet nanoparticles. Anionic HA + siRNA mixture was condensed by cationic PolyMet into negatively charged PolyMet (HA+ siRNA) complex (a, c). DOTAP/cholesterol cationic liposomes were added to the complex to form lipid coating, then DSPE-PEG and DSPE-PEG-anisamide were used to prepare a liposome using the post-insertion method to form LPH-PolyMet nanoparticles (b,d). By Zhao, et al, 2016. Used under Creative Commons Attribution 4.0.[72]

Human antigen R (HuR), a RNA binding protein, has been shown to be overexpressed in various cancers, has demonstrated its role in several oncoprotein expression regulations, and has been linked to overall resistance and poor-prognosis. Muralidharan, et al, hypothesized that cancer cell-targeted inhibition of HuR would suppress oncoproteins that would thus result in effective lung cancer therapy.[78] To examine this proposition, folate receptor-α (FRA)-targeted DOTAP:Cholesterol lipid nanoparticles carrying HuR siRNA (HuR-FNP) against human lung cancer cells were prepared and tested for stability release as shown in Figure 3. The prepared particles had a particle size of approximately 100 nm, adequately protected the siRNA from degradation, and displayed good release profiles (Figure 3b-d). HuR-FNP was shown to induce apoptotic cell death in H1299 cells that resulted in noteworthy growth inhibition and higher cell cytotoxicity.[78]

Examples of Metallic- and Carbon-based siRNA Nanocarriers

Iron oxide nanoparticles, carbon nanotubes, gold nanoparticles, and quantum dots have been developed for siRNA delivery as lung cancer therapies and diagnostic agents. Iron oxide nanoparticles theranostics have the ability to be used as a drug delivery system and a contrast agent for magnetic resonance imaging (commonly known as MRI) through the selective delivery of therapeutics agents to target sites. Carbon nanotubes have been used as drug delivery carriers because they can enter cells. Gold nanoparticles are interesting drug or siRNA delivery systems because they can be easily formed into a desired shape or size, they have exclusive surface plasmon resonance, and their surfaces may be modified through conjugation of thiolated targeting molecules.[58] Quantum dots are nanoparticulate materials having semiconductive nature which may be incorporated into living cells or tissue for experimental purposes but have been proposed for therapeutic applications as well.[79]

Lee, et al, determined whether chitosan-deoxycholic acid nanoparticles containing perfluoropentane and iron oxide can be used as an siRNA delivery system with the use of ultrasound exposure as shown in Figure 4.[80] The results show that the polymer coated iron oxide nanoparticles were able to successfully promote siRNA uptake, leading to significant apoptosis 3 days following ultrasound treatment.

Li, et al, developed a single vehicle l-arginine and hydroxypropyl-cyclodextrin quantum dot nanoparticulate combination drug delivery system containing siRNA directed towards B-cell lmphoma 2 (Bcl-2), which is a regulator of apoptosis, combined with carboplatin, doxorubicin, and paclitaxel for treatment in an A549 lung cancer cell line.[81] When compared to treatments consisting of only the free chemotherapeutics, the use of siRNA and chemotherapeutic combination loaded quantum dot nanocarriers exerted a 3 to 4 times increase in A549 cell cytotoxicity, implying improved treatment efficacy for the combination of siRNA and chemotherapeutic. These multifunctional quantum dot nanocarriers may potentially be a worthwhile method for delivering siRNA and chemotherapeutics for the lung cancer combination therapies and due to their fluorescent properties, may also serve as a diagnostic agent.

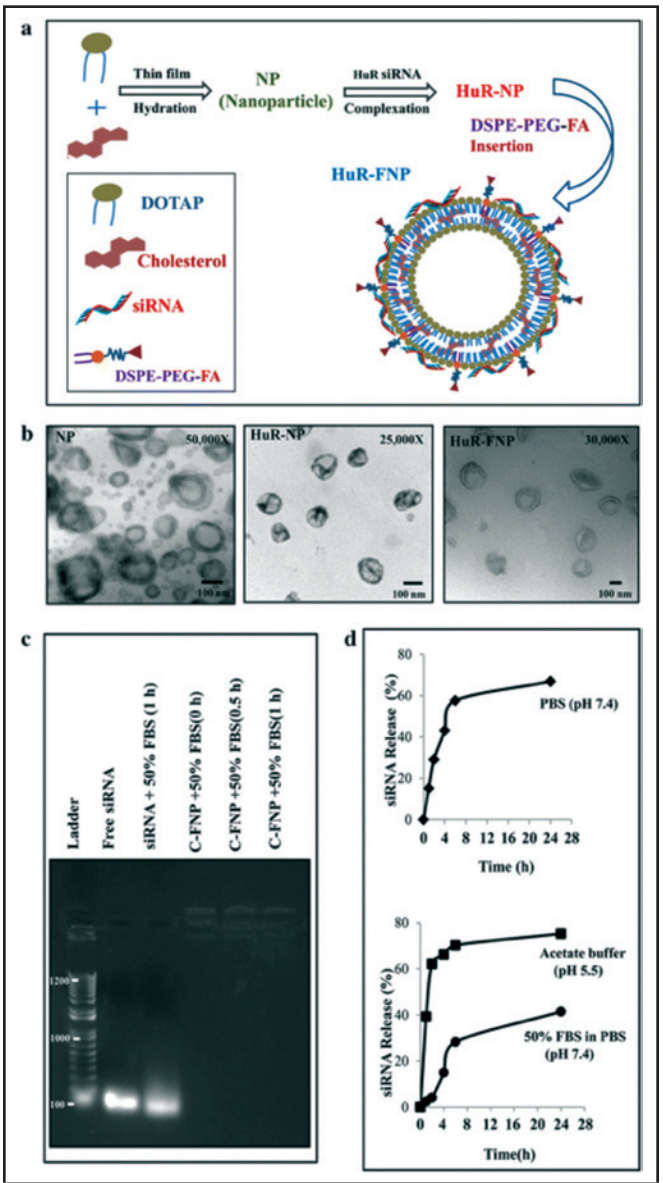

Figure 3. Synthesis and physicochemical characterization of siRNA-FNP. **a** Scheme showing HuR-FNP preparation. **b** TEM image of NP, HuR-NP, and HuR-FNP. Scale bar denotes 100 nm. **c** Agarose gel electrophoretogram showing siRNA protection by FNP at different time (0, 0.5, and 1 hr) points of incubation compared to naked siRNA exposed to serum for 1 hr. Free siRNA not exposed to serum was used as an internal marker. **d** siRNA release profile over time from siRNA-FNP in PBS (pH 7.4) measured by Quanti-iT Picogreen Assay (top figure); and from fluorescently labeled siRNA (siGLO)-FNP in acetate buffer (pH 5.5) and in 50% FBS containing PBS (pH 7.4) (bottom figure). By Muralidharanet, al, 2016. Used under Creative Commons Attribution 4.0.[78]

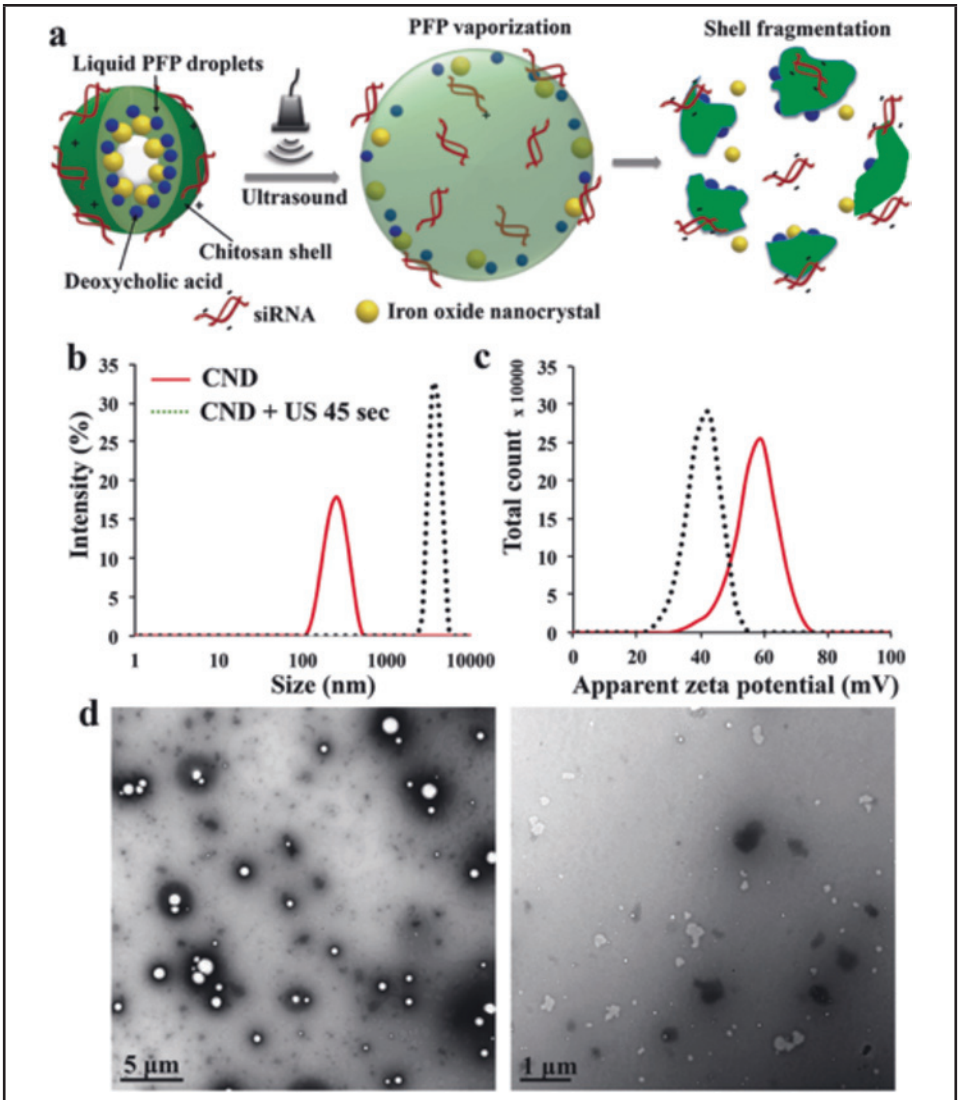

Figure 4. **a** Schematic representation of chitosan-deoxycholic acid coated perfluoropentane nanodroplets (CNDs). **b** Hydrodynamic diameters of CNDs before (solid line) and after (dotted line) exposure to ultrasound for 45 s in 10% glycerol in water. **c** Zeta potential of CNDs before and after ultrasound exposure. **d** TEM images of CND before (left) and after (right) ultrasound exposure for 45 s. By Lee, et al, 2017. Used under Creative Commons Attribution 4.0.[80]

Kamrani Moghaddam, et al, studied the ability of siRNA loaded hexagonal selenium nanoparticles (HSNM-siRNA) to prevent EGFR signaling in human NSCLC.[82] Plain hexagonal selenium nanoparticles and HSNM-siRNA were each separately used to treat NSCLC cell lines, and then onco-gene and -protein expression levels were evaluated. HSNM-siRNA was shown to downregulate the EGFR signaling gene expression and increase in a number of apoptotic cells.[82]

Mi, et al, developed a porous silicon-based nanocomposite material that simultaneously delivered chemotherapeutic agents and siRNA to the lungs after i.v. injection.[83] The silicon microparticles entrapped B-Raf proto-oncogene serine/threonine kinase siRNA-loaded liposomes and contained docetaxel entrapped polymeric nanoparticles conjugated to their surface. A synergistic antitumor effect was demonstrated when siRNA/docetaxel nanocarriers were used to treat melanoma cell cultures and also showed synergistic efficacy in vivo using a melanoma lung metastasis mouse model. The siRNA/docetaxel nanocarriers displayed higher accumulation in the lungs of the mouse model that exhibited metastatic melanoma lesions.

Wu, et al, designed multi-functionalized, integrated theranostic folate-conjugated reducible polyethylenimine passivated carbon dots (fc-rPEI-Cdots) which were used to encapsulate EGFR and cyclin B1 siRNA.[84] These particles were capable of emitting visible blue photoluminescence and siRNA intracellular delivery. In vitro cell culture studies suggested that the developed fc-rPEI-Cdots were capable of targeted siRNA delivery and were biocompatible.

Iron-oxide nanoparticles modified with biodegradable polyester nanoparticles composed of the polymers poly(lactic-co-glycolic acid) (PLGA) and PEG were loaded with telomerase siRNA. Telomerase expression is responsible for inhibition of apoptosis and cancer mutations associated with lung cancer malignant cells. This study demonstrated that the self-assembly of magnetic diblock copolymers encapsulated telomerase siRNA and resulted in reduced telomerase expression when compared to that of naked siRNA. The reduction of telomerase gene expression leads to increased tumor cell apoptotic death in lung cancer cells treated with siRNA magnetic copolymers than compared to naked siRNA treated cells.[85]

Summary and Future Directions

Nanoparticles carrying siRNA molecules have revealed high transfection rates and targeting ability for lung carcinoma tumors through systemic intravenous or localized inhaled administration. Therapeutic efficiency of gene therapy can be improved by active targeting on specific lung cancer tumors or metastases through modification or conjugation of targeting agents on the surface of the nanoparticles. The use of polymer, lipid, metals, and carbon-based nanoparticle systems in the field of targeted siRNA delivery has grown tremendously and has demonstrated promising in vitro and in vivo therapeutic efficacy results. The challenges of delivering nanoparticle mediated siRNA therapy within the body, such as maintaining the nanoparticle stability and siRNA stability, controlling the biodistribution and pharmacokinetics, penetrating biological barriers and minimizing the potential toxicity of the nanoparticles needs to be considered and overcome before entering clinical trials. The field of nanomedicine will continue to expand in the areas of cell or tissue targeting ability, circulation longevity, improved aerosol pulmonary delivery, enhanced intracellular penetration, stimuli sensitivity, and carrier-mediated visualization through using different nanocarrier properties or surface functional moieties. To increase the application of nanoparticle systems in siRNA therapy to the clinic, standards in the examination of nanoparticle safety and evaluation of therapeutic efficacy should be established to guide the direction of research and development of siRNA loaded nanoparticle therapeutic interventions.

Conflict of Interest

None of the authors identify any conflict of interest.

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THE WEATHERVANE

RUSSELL T. STODD MD; CONTRIBUTING EDITOR

THIS CRIMINAL ACTION MUST BE STOPPED.

Thirty years ago it was my good fortune to volunteer to perform eye surgery in Sudan. The Christian/Islam religious separation had yet to occur, so I was able to help patients without concern for religion. Working with two volunteer nurses, one North American and one Norwegian, I learned to my shock and dismay, after helping me their primary concern was trying to obstruct the practice of genital mutilation of female toddlers and young girls. This barbaric practice in that primitive setting performed by unwashed aunties frequently caused infections and always severe scarring. Having suffered this ugly, painful, scarring procedure themselves, mothers are reluctant to perform it on their own daughters but allow a close relative to do so. By some stretch of morality or ethics this obscene abuse is practiced for 'religious' reasons. Female genital mutilation predates Christianity and Islam and is not required in any religious text. As a result of our loosened immigration laws, now it is happening in this country. A 2012 study in the journal *Public Health Reports* estimates that more than 500,000 girls in the United States have undergone the procedure or are at risk. These children are among the most vulnerable in our society. At present only 25 states have laws that criminalize this atrocious butchery. For reasons that need explanation, the American Civil Liberties Union (ACLU) opposes the legislation. "The risk of mutilation isn't worth expanding the criminal code."

OOH. THAT REALLY ITCHES RIGHT THERE.

The rate of reports of severe allergic reactions to foods has increased by nearly five times over the past decade. This analysis was conducted by FAIR Health a New York City independent, non-profit organization that has a database of 24 billion medical and dental claims from 150 million privately insured people. James Baker MD, CEO and chief medical officer for Food Allergy Research & Education (FARE), a Virginia advocacy group, "Clearly the information suggests that not just the frequency, but the severity of food allergy attacks has increased dramatically." The proliferation in the western world, particularly to peanuts, has baffled medical experts who want to advise parents. "As many as 8% of children have food allergies with about 40% having a history of severe reactions," by FARE Health data. The study found that peanuts were the most common cause of anaphylaxis at 26% of claims. Tree nuts and seeds accounted for 18%, followed by eggs, crustaceans, and dairy. The analysis showed a greater increase in claims in rural areas than in cities, a bit of a surprise to experts. The cause for the increase may be the increased use of antibiotics, rising rates of C-sections that affect the micro-biomes of babies, and our increasingly sterile environment, like sterile wipes at the grocery store. Apparently we should do more groveling.

HERE'S NEWS TO GET YOUR ARTERIES TO RELAX.

Two drug companies (already big time) Johnson & Johnson and Bayer, jointly own the blockbuster medication Xarelto. Current research reveals that the drug when combined with aspirin reduced the risk of stroke, heart attack, amputation, or death for patients with atherosclerosis by 24% when compared with those taking aspirin alone. The trial was halted early because of Xarelto effectiveness. Analysts predict that as many as 30 million new patients may become eligible and therapy will be ongoing. Listen to the cash register ring.

NO DRIVER DOESN'T MEAN NO COMPLAINTS.

J.D. Powers, annual Initial Quality Study, is a tight follower of which companies offer the best cars. Buyers primary complaints are quality problems with semi-autonomous features, especially adaptive cruise control, autonomous braking and lane-departure guides. Auto-makers are attempting a giant leap forward trying to outrun Silicon Valley in the race to reinvent vehicle cabins. There was an average of nearly 13 complaints per 100 vehicles for the semiautonomous features, a slight uptick from 2016. J.D. Powers 2017 IQS of new cars gave high marks to Kia Motors, Genesis Motors (Hyundai luxury division) Porsche AG, Ford Motor Co and Ram (Fiat Chrysler).

CALL IT GRIT. CALL IT DETERMINATION. THERE IS NO QUIT IN THIS LADY.

In 1984 at age 27, Joan Benoit Samuelson won the women's Olympic marathon in Los Angeles. Following her triumph she continued her marathon competitions winning in Chicago and Boston in record times. Now at age sixty, one might think she would be content to just relax and rest on her multiple laurels. No way. Now she is training hard on the coast of Maine for the Bank of America Chicago Marathon in October. She is not content planning to win, but wants to be the first female sexagenarian to break three hours. She proves it is possible to be an athletic inspiration to the grandchildren when she might be planning how to spend her social security.

WE NEED A DUI TEST FOR MARIJUANA.

In Washington state an 18-year-old girl was killed in a motor vehicle crash. The offending driver admitted he was smoking marijuana and that his driving ability was impaired. Without his confession he could not be found guilty of DUI since no reliable test exists for on-the-spot marijuana intoxication. Urine tests, used widely for employment tests, do not test for impairment. The breakdown products of tetrahydrocannabinol, or THC, the psychoactive component, can be found months after a high has worn off. The only test to date that shows any promise for detecting intoxication is blood plasma level. Empowering police officers to draw blood at the roadside is not likely to happen. Moreover, it would be a dangerous precedent for individual liberties. The possibility of a "breathalyzer" for marijuana may hold merit, but even if practical, no level of substance impairment (like 0.08% for alcohol) is available. Much research needs to be done, and Congress should encourage it now with research money.

ADDENDA

- An average person will wait 40 seconds for an elevator before fidgeting.
- Each year 30,000 silver teaspoons are stolen from the Washington, D.C. Hilton.
- Thomas Jefferson's slaves loved him so much they called him a special name, "Dad."
- Voters want a fraud they can believe in.
- I'm a hypochondriac, but I manage to control it with a placebo.
- Do you know how Columbus discovered America? He was attracted by the lights from the Indian Casinos.
- Talk is cheap until you hire a lawyer.
- Henry James writes fiction as if it were a painful bowel movement.
- I am at two with nature.

ALOHA AND KEEP THE FAITH rts

(Editorial comment is strictly that of the writer.)

WRITING CONTEST

HAWAI'I JOURNAL OF MEDICINE & PUBLIC HEALTH

The Hawai'i Journal of Medicine & Public Health invites students and professionals at public health, medical, nursing, pharmacy, and dental schools or programs to enter in its **3rd Annual Writing Contest**.

Submissions must be original works related to the practice of medicine or public health, with a focus on Hawai'i or Pacific Rim region.

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Applicants must have an advisor who can attest to the individual's contributions and provide final approval.

DEADLINE 12/29/17

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