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Investigating Approaches to Improving Appropriate Antibiotic Use Among Higher Risk Ethnic Groups

Dana L. Alden PhD; Alan Tice MD, FACP; and John T. Berthiaume MD, FACP

Abstract

A field study with follow up investigations sought to: 1) determine whether cold packs (over-the-counter symptomatic treatments), coupled with in-office education, improve antibiotic-related knowledge, attitudes and behaviors more than in-office education alone in patient populations with high percentages of Asian Americans and Hawaiian/Pacific Islanders; 2) identify possible reasons for intervention outcomes as described by physicians who participated in the field study; and 3) explore potential future directions based on a large sample survey of physicians in the field study’s highly ethnic county. The intervention resulted in a pre- to post-consultation decrease in perceived need for and an increase in knowledge about antibiotic risks but had no impact on frequency of reported receipt of an antibiotic prescription. Unexpectedly, in-office education alone was more effective in increasing knowledge than in-office education plus the cold pack. In-depth interviews of field study physicians and a large scale physician survey suggest that cold pack interventions targeting patient populations with high percentages of Asian Americans and Hawaiian/Pacific Islanders may be more likely to succeed if accompanied by mass public education regarding risks and physician training regarding effective ways to talk to patients. Use of in-office education with cold packs alone may not achieve desired results.

Introduction

Inappropriate antibiotic use for treatment of upper respiratory infections (URI) remains a critical public health issue in the United States and many other countries and is particularly acute among certain ethnic subpopulations. In cooperation with primary care physicians, a field study examined alternative strategies for reducing inappropriate use of antibiotics in Honolulu City and County — a region in which the majority of residents are either Asian American or Hawaiian/Pacific Islanders. The field study compares two approaches to reducing inappropriate antibiotic use: providing in-office education about the dangers of inappropriate antibiotic use versus providing in-office education plus a free “cold pack” containing over-the-counter symptomatic treatments. Post-intervention interviews with participating physicians and a survey of area primary care physicians sought to understand reasons for field study outcomes.

A recent in-depth review of 22 national and 6 regional campaigns in high income countries to improve antibiotic use found evidence of positive effects but that evidence was mixed. For example, a study in Colorado found a reduction in antibiotic (ABX) use in a community (versus a control community) following a mass media campaign in that area. However, a statewide campaign in Wisconsin failed to reduce ABX prescription rates more than in a control state without such a campaign. In the in-depth review, only one intervention using a combination of education and in-office substitute products such as the cold pack is mentioned but it appears that evaluative data on related outcomes has not been published. Thus, despite some indication of the positive effects of public education, mixed evidence and the absence of published quasi-experimental research examining the impact of cold packs in conjunction with education suggests the importance of further research.

The need for additional research is particularly acute for patient populations with high percentages of ethnic minorities and newly arrived immigrants as are found in the state of Hawai‘i. For example, a random sample survey of different ethnicities in Hawai‘i found that self-identified Filipinos have lower levels of ABX knowledge, express higher perceived ABX need, and report more frequent ABX use. Whites were found to be at the opposite end of these indicators with other Asian-American groups (Japanese, Chinese, and Korean) and Hawaiian/Pacific Islanders scoring in-between. This study also found that Filipinos and Japanese Americans preferred an interaction style with their physician characterized by lower levels of information exchange between both parties. The researchers suggest that interventions in such highly ethnic patient populations may benefit from use of a tangible product that serves as a substitute for an antibiotic prescription and fosters patient-physician communication about URI treatment and antibiotics. Tangible products are often used in social marketing interventions. Most often, the purpose of tangible products is to facilitate and enhance the impact of education and other tactics on healthful behavior change. Testing the hypothesis that in-office education plus a cold pack (EDCP) will increase knowledge, improve attitudes and reduce reported receipt of an ABX prescription more than in-office education alone (ED) in a patient population with high percentages of Asian Americans and Hawaiian/Pacific Islanders, the following field study was undertaken.

Methods

Eight Asian American primary care physicians with independent clinical practices were selected based on 1) higher than average prescription rates as indicated in the records of the State’s largest private insurance provider and 2) practice location, specifically in areas of Honolulu City and County with high proportions of Asian Americans and Hawaiian/Pacific Islanders. Four physicians participated in the ED treatment and four physicians participated in the EDCP treatment.

The education treatment for both groups consisted of a brochure entitled, “Antibiotics — Did You Know?” The brochure contained basic information about bacterial versus viral infection with cartoon schematics and photos regarding URI and antibiotics. Patients with additional questions were urged to talk with their doctor about the risks of antibiotics. A concluding comment noted that “Antibiotics are not always the answer.” All study procedures and materials were reviewed and approved by the human subjects committee of the University of Hawai‘i.

The cold pack’s design and contents were based on input from focus groups with Asian American and Pacific Islander patients as well as internal medicine physicians who routinely treat ethnic patients in Honolulu County for URI. The kit included products designed to provide symptomatic relief identified by the targeted ethnic population and approved by the physicians. The products (Tylenol®, lemon throat lozenges, instant chicken soup packets and ginger tea) were placed inside a zip lock bag and lined with...
colored paper to provide a professional look while maintaining the low cost nature of the intervention. Cold pack physicians each received 100 cold packs for use over the three week study period and were asked to briefly describe the cold pack’s contents and the benefits of treating symptoms without ABX. They were also asked to only give the cold pack to a patient when they had determined that viral infection was probable and that symptomatic relief was the most appropriate treatment.

Patients were asked to complete a pre-consultation questionnaire that measured: patient knowledge; attitudes and practices with respect to URI infection and treatment; and demographic characteristics. They were also asked to read the ABX educational brochure. Following their visit with the physician, patients completed a post-consultation questionnaire that included objective measures of knowledge and subjective measures regarding treatment of URI. Established scales8,10,11 were used to compare treatment groups on ABX attitude/knowledge and reported receipt of an ABX prescription using t-tests, chi-square statistics and MANOVA.

Of the 299 adult patients with URI symptoms who completed surveys during the study period, 147 were in the ED treatment and 152 were in the EDCP treatment. The mean age was 45.6 with a range from 19 to 89. A large majority (71%) reported total family incomes between $25,001 and $125,000. Major ethnic groups included East and Southeast Asians (primarily Japanese, Chinese, Koreans; 45.3%); Filipinos and Hispanics (34.2%); Hawaiian and South Pacific Islanders (10.2%); Whites and Blacks (7.2%); and missing (3%). Age, marital status, gender, education and major group ethnicity did not vary significantly by treatment. Differences across treatment were significant for household income (p<0.023) and primary occupation (p<.02), but, the directional association as indicated by Goodman-Kruskal lambda (λ) was not statistically significant (p>0.70).

**Results**

**Pre-Consultation**

Perceived need for ABX in treating URI was measured with a multi-item 7-point scale used in several studies.8 A higher score indicates greater perceived need and thus, a more positive attitude toward ABX (Chronbach’s alpha = 0.89). Pre-consultation attitudes toward ABX were positive (i.e., significantly greater than the midpoint, t-test, P<0.045) and did not differ by treatment group. Only 11% of the subjects stated that they never used ABX to treat URI, while 86% reported using them one or more times a year. There were no significant differences across treatment in terms of reported ABX use, how well they felt that day, and their overall perceived state of health. A multi-item scale (see Table 1) assessing pre-consultation knowledge of appropriate ABX use indicated low levels of knowledge that did not vary significantly by treatment group.

**Table 1.— Antibiotic Knowledge Questions**

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antibiotics should be used to treat only viral infections.</td>
<td>1</td>
</tr>
<tr>
<td>2. Antibiotics should be used to treat only bacterial infections.</td>
<td>2</td>
</tr>
<tr>
<td>3. Cough, cold and flu illnesses are most often caused by viruses.</td>
<td>3</td>
</tr>
<tr>
<td>4. Cough, cold and flu illnesses are most often caused by bacteria.</td>
<td>4</td>
</tr>
</tbody>
</table>

*7-point “Agree-Disagree” scale collapsed to binomial measure with “don’t knows” included with those who agreed or disagreed incorrectly with the statement. Using this approach, only 6% of respondents answered all four questions correctly.

**Post-Consultation**

Pre- versus post-consultation t-test analyses for the overall sample found that “perceived need for ABX” significantly decreased (P <0.001) and patient knowledge of appropriate ABX use significantly increased (P <0.034). To determine whether the "in-office education plus cold pack" (EDCP) when compared with “in-office education only” (ED) treatment resulted in more positive ABX attitudes and knowledge, MANOVA analysis was undertaken. Although the multivariate model was significant (P <0.007), univariate analysis indicated that this was primarily due to an increase in knowledge from pre- to post-consultation (F=8.7, degrees of freedom = 282, P <.003) rather than other outcome measures such as ABX attitude change (P=0.098). Furthermore, t-test analysis of the pre-consultation versus post-consultation means revealed that the increase in appropriate ABX use knowledge was significantly larger for the ED group (P<0.002) but not the EDCP group.

Within the EDCP group, t-tests indicate that patients who reported receiving the cold pack (28/152) were significantly more satisfied with their consultation (P<0.001) and with their physician (P<0.001) when compared with the “education only” group. They also became marginally more negative in their attitudes toward antibiotics (P<0.062). However, it is not possible to know the causal direction suggested by these results, i.e., whether giving the cold pack increased satisfaction or the physician chose to give the cold pack to patients who appeared more satisfied. Finally, chi-square analysis revealed that EDCP patients reporting receipt of the cold pack did not significantly differ from the ED group in terms of obtaining a prescription.

These results raise many questions regarding the cold pack’s failure to stimulate additional discussion between patient and physician, improve knowledge, reduce positive ABX attitudes overall and produce fewer ABX prescriptions. Furthermore, given that only 18.4% of EDCP patients reported receiving a cold pack and that more than half of these patients also received an ABX prescription, one may question physician willingness to substitute over-the-counter symptomatic relief for prescriptive ABX treatment. Seeking clarification, two follow up investigations were undertaken. First, all eight physicians were interviewed to learn more about possible reasons for the intervention results. Second, a questionnaire was administered to a large sample of Honolulu County physicians who treat URI.

**Follow-up Interviews with Field Study Physicians**

Several field study physicians stated that the cold pack would have been more effective if the study had taken place over a longer time period. Others commented that, regardless of the study’s timeframe, the cold packs were “just too much trouble” to use though none suggested that appearance or ingredients posed a problem. No comments regarding greater or lesser challenges for one ethnic group versus another arose during the interviews. Physician responses indicated that a majority believed public education regarding ABX risk would increase physician willingness to substitute cold pack product instead of a prescription. The fact that only one physician mentioned the need for improvement of physician communication skills suggests that field study physicians generally viewed inappropriate ABX use as a patient issue rather than a physician problem.
Follow-up Cross-Sectional Physician Survey

A questionnaire was administered to Honolulu County physicians to determine whether they agreed with the field study physicians’ assessments and to identify potential solutions to the challenge of reducing inappropriate ABX use for treatment of URI in an area with large Asian American and Pacific Islander populations. A complete listing of primary care physicians in Honolulu County likely to see URI patients was obtained from the Hawai‘i State Department of Health. A cover letter and questionnaire were mailed to 900 physicians on the list. The cover letter informed physicians of the results from the cold pack intervention and the eight participating doctors’ opinions regarding reasons for the outcomes (Table 1).

Confirming thoughts expressed by the field study physicians, respondents ranked a mass media campaign targeting the general public as the most effective intervention in terms of reducing inappropriate ABX use (Table 3). This was followed by interventions that would: 1) encourage physicians to tell patients directly about appropriate ABX use, 2) place printed and poster materials in patient waiting rooms, 3) distribute cold packs as alternatives to ABX for URI, and 4) promote the use of alternative strategies for different patient populations, e.g., delaying ABX coverage for younger, healthier patients rather than every patient. While statistically different from the midpoint, physician attitudes toward the cold pack intervention ($\chi^2 = 3.3$) were very close to neutral. Interventions judged least effective were: 1) promoting use of a delayed prescription to be filled in 2-3 days, 2) providing physicians with more information about the risks of ABX, and 3) promoting physician decision-making based on cultured pathogen identification.

**Discussion**

This study compared “in-office education” (ED) with “in-office education plus cold pack” (EDCP) in a field study that involved eight primary care practices with relatively high ABX prescription rates and relatively high percentages of Asian Americans and Hawaiian/Pacific Islanders. The EDCP intervention performed less effectively than the ED treatment, which accounted for a majority of the significant overall improvement in patient knowledge regarding ABX use. Follow up interviews with the eight field study physicians

<table>
<thead>
<tr>
<th>Table 2.— Descriptive characteristics of surveyed physicians</th>
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<tbody>
<tr>
<td>Physician Sample Size</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Physician Average Age</td>
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<tr>
<td>Average Number of Years in Practice</td>
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<tr>
<td>Physician Gender</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Missing</td>
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<table>
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<tr>
<th>Table 3.— Ranked physician evaluations of potential interventions to reduce inappropriate antibiotic use</th>
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</thead>
<tbody>
<tr>
<td>Average Rating* (5-point scale)</td>
</tr>
<tr>
<td>Conduct a mass media campaign on radio, TV, newspaper directed at the general public regarding appropriate antibiotic use</td>
</tr>
<tr>
<td>Encourage physicians to tell patients directly about appropriate antibiotic use</td>
</tr>
<tr>
<td>Provide printed and poster educational materials in patient waiting rooms regarding appropriate antibiotic use</td>
</tr>
<tr>
<td>Promote use of a cold pack (symptomatic therapy with anti-pyretic, antihistamine and chicken soup or equivalent) as an alternative to antibiotics for URI</td>
</tr>
<tr>
<td>Promote use of different approaches for different patient populations, e.g., delaying antibiotic coverage for younger, healthier patients rather than every patient</td>
</tr>
<tr>
<td>Promote idea of asking the patient to call back in two or three days for an antibiotic prescription if symptoms persist or worsen</td>
</tr>
<tr>
<td>Provide video educational programs in patient waiting rooms regarding appropriate antibiotic use</td>
</tr>
<tr>
<td>Provide physicians with more information about the adverse effects of antibiotic therapy</td>
</tr>
<tr>
<td>Promote taking of a culture and prescribing an antibiotic only if a bacterial pathogen is found</td>
</tr>
<tr>
<td>Promote use of a “delayed prescription” to be filled in 2-3 days or antibiotics should URI symptoms not improve or worsen</td>
</tr>
</tbody>
</table>

*5-point scale with 5 = “most effective” and 1 = “least effective”
indicated that they perceived mass education about ABX risk as a pre-intervention need. Thus, a combination of physician concerns about patient understanding of cold pack substitution for ABX and ability to “sell” the cold pack concept to those patients may have led to the intervention’s failure. While future research may result in refinement of cold pack contents so that the packs themselves are more appealing to physicians, perceived “selling” of the pack appears problematic and may prove easier in conjunction with a mass public health education campaign. It is important to note that our physician sample was purposively selected and thus, the findings apply most directly to physicians with relatively high ABX prescription rates and relatively high percentages of Asian American and Hawaiian/Pacific Islander patient populations.

However, it should also be noted that a county-wide survey of physicians in Honolulu found that they also thought that public health education and physician training on more effective communication were needed. Even so, contrary to the high numbers of physicians reporting receipt of ABX prescriptions in the field study, surveyed physicians strongly supported symptomatic treatment and waiting to see if ABX were necessary when presented with different case studies. Tempered by the fact that field study physicians were higher than average ABX prescribers, the survey suggests that a gap may exist between physicians’ aspirations and their actual behavior when faced with an ill patient in predominantly Asian American and Hawaiian/Pacific Islander communities.

Emphasis on public health education via the mass media and in the physician’s waiting room, coupled with physician continuing medical education (CME) training, may constitute effective strategies. CME lectures were rated most positively along with the “observations of infectious disease consultants.” Attitudes toward other sources such as mailings from the Centers for Disease Control, mailings from the State Department of Health and quarterly reports on ABX prescriptions from the State’s major health insurance company were rated as neutral or negative.

The fact that there were few differences between the ED and EDCP treatment groups, coupled with high measure reliabilities and use of established scales, suggests that the field study possessed fairly high internal validity. Of course, this validity is limited to the predominantly Asian and Hawaiian/Pacific Islander ethnic segments involved but there is no reason to believe that it would not extend to ethnic segments with similar cultural orientations. In addition, the physician survey sample was not a census, pointing to the importance of replication. Even so, the repeated finding in the follow up studies of the perceived need for additional physician training on communicating more effectively the costs and benefits of ABX suggests an important topic for future research. These findings are in line with the stream of research on reducing inappropriate ABX use referred to earlier, which points to the likelihood that a multidimensional effort is needed involving mass public education, in-office education, substitute products such as cold packs, and physician CME training on effective communication with their patients regarding proper ABX use. Of course, these conclusions seem most appropriate for addressing ABX misuse in patient populations comprised of high percentages of Asian Americans and Hawaiians/Pacific Islanders but, given past research, the importance of a multi-pronged and sustained effort in general appears clear. While the problem of inappropriate ABX prescriptions remains a major challenge, this study in combination with the broader literature stream suggests potential directions for future research and progress.

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Ph: (808) 956-8565
Email: dalden@hawaii.edu

References

Hoʻomau: to persevere, to be persistent
**Diagnostic Value of Urine Sodium Concentration in Hyponatremia Due to Syndrome of Inappropriate Antiuretic Hormone Secretion Versus Hypovolemia**

Takashi Hato MD and Roland Ng MD

**Abstract**

**Background:** We are often left with the differential diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH) versus hypovolemic hyponatremia. It is difficult to tell who will respond to isotonic saline infusion and who will not, if the urine sodium value is not completely suppressed (>10 mEq/L). Further, we investigated the usefulness of urine fluid management if the value is not completely suppressed (i.e., sodium can still be used to guide initial diagnosis and subsequent management). The intention of this study was to examine whether the urine sodium value was clinically meaningful in separating SIADH from hypovolemia. It is difficult to tell who will respond to isotonic saline infusion and who will not, if the urine sodium value is not completely suppressed (>10 mEq/L).

**Methods:** The diagnostic accuracy of the urine sodium value was compared to that of a complete work-up and hospital course, including a response to saline infusion in patients with a final diagnosis of SIADH or hypovolemic hyponatremia. We also examined the diagnostic value of urine sodium-to-BUN ratio which should improve separation between SIADH and hypovolemia since the urine sodium and BUN move in opposite directions in these two conditions.

**Results:** The urine sodium value of 50 mEq/L was the most accurate in separating SIADH from hypovolemic hyponatremia: sensitivity 0.89, specificity 0.69, and accuracy 0.82. The diagnostic utility for SIADH versus hypovolemia, as quantified by the areas under the ROC curves, was not statistically different between urine sodium alone (0.89, 95% CI 0.77-0.96) and urine sodium-to-BUN ratio (0.93, 95% CI 0.83-0.98); p-value 0.33.

**Conclusions:** When the underlying cause is inconclusive between SIADH and hypovolemia, and when only basic laboratory results are available at the time of initial evaluation, the urine sodium alone will be adequate to guide initial fluid management. In contrast to traditional teaching, elevated urine sodium levels up to 50 mEq/L demonstrated clinically meaningful responses to isotonic saline infusion.

**Introduction**

A small amount of literature suggests that the use of complex indices would be helpful to distinguish SIADH patients from others (e.g., combined use of fractional excretion of sodium and fractional excretion of urea). However, in the real world, most physicians only order the urine sodium and then start intravenous fluids to correct hyponatremia once patients are noted to be hypotensive. However, it is often difficult to tell who will respond to isotonic saline infusion and who will not. While it is relatively easy to exclude hypervolemic hyponatremia due to renal disease, heart failure, or liver disease just by history and physical examination, generally we are left with the differential diagnosis of SIADH versus hypovolemic hyponatremia. Urine sodium alone is likely enough to guide our management in patients who have extreme values (urine sodium concentration below 10 mEq/L, suggesting a good response to isotonic saline). But how about a urine sodium level of 40 mEq/L in the face of diuretic use?

The intention of this study was to examine whether the urine sodium can still be used to guide initial diagnosis and subsequent fluid management if the value is not completely suppressed (i.e., >10 mEq/L). Further, we investigated the usefulness of urine sodium-to-BUN ratio as a discriminative index between SIADH and hypovolemic hyponatremia. Since the urine sodium and BUN move in opposite directions (higher urine sodium and lower BUN levels tend to occur in SIADH as opposed to lower urine sodium and higher BUN in hypovolemia), the ratio should magnify the differences between these two conditions and improve separation of SIADH from hypovolemia.

**Methods**

The diagnostic accuracy of urine sodium value was compared to that of a complete work-up and hospital course. The final discharge diagnosis, which was based on all available clinical, laboratory, and imaging findings, and the overall hospital course, was made by consultant nephrologists. The study was a retrospective chart review conducted at a university-affiliated hospital. The study was approved by the local investigational review board. Cases were limited to ones in which nephrologists were involved in consultation to maintain uniformity and accuracy of the diagnosis of SIADH versus hypovolemia.

The authors identified a total of 78 cases of hyponatremia that were evaluated by independent nephrologists in consultation over a 5-year period (2005-2009). Forty five cases met the predefined inclusion and exclusion criteria. Inclusion criteria were as follows: 1) Sodium concentration below 130 mEq/L at the time of nephrology consultation. 2) Serum osmolality less than 280 mOsm/kg H2O. 3) A patient with a final diagnosis of either SIADH or extracellular volume depletion documented by consultant nephrologists based on the entire hospital course. 4) A patient who received an isotonic saline infusion. Hyponatremia due to causes other than SIADH and hypovolemia were excluded from the study (adrenal, thyroid, or pituitary insufficiency, chronic kidney disease, nephrotic syndrome, cirrhosis, congestive heart failure, polydipsia, or low solute “beer potomania,” etc). Since the primary interest of this study lay in cases where SIADH or hypovolemia could not easily be separated, obvious cases were excluded: urine sodium <10 mEq/L with consistent clinical findings. Those who did not have the urine sodium measured in a timely manner were excluded. In the absence of a single gold standard diagnostic test, the response to an infusion of isotonic saline and the subsequent hospital course yield invaluable information, which often unmasks the cause of the hyponatremia. The threshold for a “good response” to an isotonic saline infusion was not pre-specified because this was a retrospective study. Consultant nephrologists were aware of the results of the urine sodium and BUN values. However, they were not aware that there would be a retrospective study in using urine sodium and BUN values at that time. The rate of initial isotonic saline infusion varied anywhere from 75 ml/h to 1 L of bolus. Some of the urine and serum laboratory values were obtained during saline infusion rather than pre-infusion, but none of the values were obtained after correction of hyponatremia.
**Statistical Analysis**

Continuous variables are presented as means (±SD), and categorical variables as numbers and percentages. Continuous variables were compared with the use of the Welch two sample t-test, and categorical variables with the use of Pearson’s Chi-squared test and Fisher’s exact test. Logistic regression analysis was used to adjust confounders and to examine correlations among urine sodium, BUN, renal function, diuretic use, and other pertinent parameters. Receiver-operating-characteristic (ROC) curves were constructed to assess the sensitivity and specificity of urine sodium value and urine sodium-to-BUN ratio, and ability to diagnose SIADH and hypovolemic hyponatremia at the time of hospitalization. The comparison of areas under the ROC curves (AUC) was performed as a nonparametric approach. Statistical analyses were performed using R software 2.9.0.

**Results**

A total of 45 cases met the predefined criteria for inclusion. Twenty nine cases were assigned the final diagnosis of SIADH, and 16 cases were hypovolemic hyponatremia. Baseline characteristics are shown in Table 1. At the start of hospitalization, 24 out of 45 patients (53%) were thought to have hypovolemic hyponatremia. However, based on the hospital course, including an inadequate response to saline infusion, and additional workup, the final diagnosis of hypovolemic hyponatremia at the time of discharge was reduced to 16 cases out of 45 (36%).

Baseline characteristics were well matched. The majority of the patients were elderly Asians. Falls and loss of balance with subsequent trauma were frequent causes for seeking medical attention. Unspecified weakness was also a common chief complaint. There was no statistical difference in the presence of neoplasm, pulmonary disease, and use of antipsychotics and antidepressants, but they trended toward a diagnosis of SIADH. The most common neoplasm was acute myeloid leukemia and lymphoma (3 cases), followed by pancreatic carcinoma (2 cases), and non-small cell lung cancer (1 case). The breakdown of pulmonary disease consisted of pneumonia (7 cases), exacerbated chronic obstructive pulmonary disease or interstitial lung disease (4 cases), and adult respiratory distress syndrome (2 cases). Often the underlying etiology of vomiting was not determined. There was a statistical difference in the greater use of diuretics with hypovolemia as compared with SIADH. Furosemide was used in 6 cases, hydrochlorothiazide in 10 cases, and spironolactone in 3 cases. Some patients were on multiple diuretics. Diuretic use had little effect on urine sodium concentration (Table 2). There was a difference in initial serum creatinine values and estimated glomerular filtration rates with MDRD (Modification of Diet in Renal Disease). However, serum creatinine levels improved faster in hypovolemic hyponatremia compared with SIADH. Twenty-nine cases were assigned the final diagnosis of SIADH, and 16 cases were hypovolemic hyponatremia. Twenty-nine cases were assigned the final diagnosis of SIADH, and 16 cases were hypovolemic hyponatremia. The comparison of areas under the ROC curves (AUC) was performed as a nonparametric approach. Statistical analyses were performed using R software 2.9.0.

**Table 1.— Characteristics of Patients with SIADH and Hypovolemia**

<table>
<thead>
<tr>
<th></th>
<th>SIADH</th>
<th>Hypovolemia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>81.0 ± 9.2</td>
<td>79.3 ± 8.1</td>
<td>0.514</td>
</tr>
<tr>
<td>Gender – male sex – no. (%)</td>
<td>12 (41)</td>
<td>6 (37.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Chief complaints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered mental status – no. (%)</td>
<td>8 (27.6)</td>
<td>2 (12.5)</td>
<td>0.292</td>
</tr>
<tr>
<td>Fall – no. (%)</td>
<td>8 (27.6)</td>
<td>2 (12.5)</td>
<td>0.115</td>
</tr>
<tr>
<td>Bone fracture – no. (%)</td>
<td>5 (17.2)</td>
<td>12 (82.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Acute pain – no. (%)</td>
<td>14 (48.3)</td>
<td>5 (31.3)</td>
<td>0.429</td>
</tr>
<tr>
<td>Intracranial event – no. (%)</td>
<td>2 (6.9)</td>
<td>0 (0)</td>
<td>0.531</td>
</tr>
<tr>
<td>Vomiting – no. (%)</td>
<td>5 (17.2)</td>
<td>3 (18.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Underlying condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease (non malignant) – no. (%)</td>
<td>10 (34.5)</td>
<td>1 (6.2)</td>
<td>0.067</td>
</tr>
<tr>
<td>Neoplasm – no. (%)</td>
<td>6 (20.7)</td>
<td>2 (12.5)</td>
<td>0.692</td>
</tr>
<tr>
<td>Use of antipsychotics antidepressants – no. (%)</td>
<td>8 (27.6)</td>
<td>2 (12.5)</td>
<td>0.292</td>
</tr>
<tr>
<td>Diuretic use – no. (%)</td>
<td>5 (17.2)</td>
<td>10 (62.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Biochemical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine - mg/dL</td>
<td>0.78 ± 0.23</td>
<td>1.06 ± 0.28</td>
<td>0.001</td>
</tr>
<tr>
<td>Estimated GFR (MDRD) – mL/min</td>
<td>94.1 ± 31.4</td>
<td>66.8 ± 25.0</td>
<td>0.003</td>
</tr>
<tr>
<td>BUN – mg/dL</td>
<td>13.2 ± 6.3</td>
<td>24.1 ± 12.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum Na (0h) – mEq/L</td>
<td>120.8 ± 5.3</td>
<td>123.3 ± 5.7</td>
<td>0.153</td>
</tr>
<tr>
<td>Serum Na (24h) – mEq/L</td>
<td>123.8 ± 5.7</td>
<td>131.2 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Na (48h) – mEq/L</td>
<td>126.9 ± 4.5</td>
<td>135.0 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial Urine Na – mEq/L</td>
<td>85.1 ± 31.4</td>
<td>40.3 ± 23.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine Na/BUN ratio</td>
<td>8.6 ± 6.7</td>
<td>2.0 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine osmolarity – mOsm/kg</td>
<td>424.8 ± 158.4</td>
<td>307.1 ± 192.6</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Note: Plus-minus values are means ± SD

* Logistic regression model, adjusted for glomerular filtration rate and diuretic use

**Table 2.— Urine Sodium Values in Patients with SIADH and Hypovolemia in Relation to Diuretic Use**

<table>
<thead>
<tr>
<th>Urine Na value</th>
<th>Diuretic use = Yes</th>
<th>Diuretic use = No</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH – mEq/L</td>
<td>78.6 (n=5)</td>
<td>86.5 (n=24)</td>
<td>0.503 a</td>
</tr>
<tr>
<td>Hypovolemia – mEq/L</td>
<td>44.2 (n=10)</td>
<td>33.8 (n=6)</td>
<td>0.367 a</td>
</tr>
</tbody>
</table>
The urine sodium value at presentation was significantly higher in patients with SIADH. The BUN value alone was not robust enough after adjusting for the use of diuretics and glomerular filtration rates (p-value 0.061). Urine sodium-to-BUN ratio was significantly higher in patients in whom SIADH was the final diagnosis than in patients in whom the final diagnosis was hypovolemic hyponatremia (Table 1 and Figure 2). However, the diagnostic utility for SIADH versus hypovolemia, as quantified by the AUC, was not statistically different between urine sodium alone (AUC 0.89, 95% CI 0.77-0.96) and urine sodium-to-BUN ratio (AUC 0.93, 95% CI 0.83-0.98) (Figure 3). The urine sodium value of 50 mEq/L conferred the best accuracy in separating SIADH from hypovolemic hyponatremia: sensitivity 0.89, specificity 0.69, and accuracy 0.82.

**Discussion**

The primary purpose of our study was to compare the diagnostic accuracy of urine sodium value to that of a complete work-up and hospital course including a response to isotonic saline infusion. We
also examined the diagnostic value of the urine sodium-to-BUN ratio which should magnify the differences between SIADH and hypovolemia. The urine sodium value of 50 mEq/L conferred the best accuracy in separating SIADH from hypovolemic hyponatremia. The study demonstrated that the urine sodium-to-BUN ratio was not particularly useful to distinguish SIADH from hypovolemic hyponatremia when compared with the urine sodium alone as quantified by the AUC.

The therapeutic response to isotonic saline is the best available tool to distinguish SIADH from hypovolemic hyponatremia. However, the distinction should not be based solely on the response to isotonic saline. The clinical scenario in a patient with hyponatremia is often complex, and there may be a component of both SIADH and hypovolemia. Without various factors taken into account, it is impossible to arrive at a proper diagnosis. It is not uncommon to see some improvement in the serum sodium concentration with isotonic saline infusion in the setting of SIADH. Overall, the magnitude of the response to saline infusion was clearly higher in patients with hypovolemia as opposed to patients with diagnosis of SIADH. We did not incorporate patients with urine sodiums below 10 mEq/L. In the presence of extremely low urine sodiums and a low to normal volume status, there is no doubt in the usefulness of saline infusion. Since we wanted to know the value of saline infusion in cases in which the urine sodium was not completely suppressed, we omitted those who had extremely low urine sodium values. In actuality, only 3 cases were removed from analysis because of undetectable urine sodium levels. This may be a reflection of selection bias in that simple, obvious cases of hypovolemic hyponatremia supported by very low urine sodiums did not come to the attention of nephrologists.

In patients with urine sodiums below 50 mEq/L, the mean increase in serum sodium within a 48 hour period was 12.1 mEq/L. With urine sodiums above 50 mEq/L, the mean increase was 5.3 mEq/L. The results corresponded well to the magnitude of increase in serum sodium level based on the final diagnosis: 11.7 mEq/L of increase in patients with hypovolemia, 6.1 mEq/L of increase in patients with SIADH. For all practical purposes, the urine sodium can be used as a good indicator as to what to expect with an initial saline infusion. In other words, the diagnostic accuracy of 82% (urine sodium at 50 mEq/L) is clinically satisfactory from the standpoint of initial fluid management. Complicated diagnostic tools such as urine sodium-to-BUN, fractional excretion of sodium, uric acid, and urea will have little additional impact clinically. Traditionally, a urine sodium of 20 or 30 mEq/L is used as a cutoff value to differentiate whether a patient would respond to isotonic saline infusion or not. In our study, the urine sodium at 20 mEq/L provided a very low specificity and failed to distinguish SIADH and hypovolemia (Figure 3). This difference may be due to the average age of the study population, which at 80 years, may have slow adaptation to hypovolemia with reduction of urinary sodium.

Finally, there are several limitations in our study. It is a retrospective study, and we were unable to control several aspects. All of the patients received isotonic saline; however, the rate of IV fluid varied from 75 mL/L to 1 liter of bolus. Most received an isotonic saline infusion at a rate of 100 to 150 mL/hour initially. The timing of the nephrology consultation varied, and measurement of relevant laboratory values was not exactly every 24 hours. Another limitation of the study is that these patients were all selected cases seen by nephrology specialists. These cases were probably more complicated and may not be generalizable to ones seen by emergency department physicians or general internists. Consultant nephrologists were aware of the results of the urine sodium and BUN values, and one might question the validity of this study if they heavily relied on these values in making the diagnosis. The nephrologists were not aware that there would be a retrospective study in using the urine sodium and BUN values at that time. Also, the fact that many patients were categorized into hypovolemia despite a high urine sodium level (in a traditional perspective) speaks against this concern.

Conclusion

The ability to distinguish SIADH and hypovolemia using the urine sodium alone was reasonably high (the accuracy with a cutoff value of 50 mEq/L was 82%). In contrast to traditional teaching, elevated urine sodium levels up to 50 mEq/L demonstrated clinically meaningful responses to isotonic saline infusion. When the underlying cause is inconclusive between SIADH and hypovolemia, and when only basic laboratory results are available at the time of initial evaluation, the urine sodium alone will be adequate to guide initial fluid management.

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References
Detection of BRCA1 and BRCA2 Mutations in a Selected Hawai‘i Population

Michael E. Carney MD; Michele S. Basiliere MS, CGC; Kiley Mates BS; and Christina K. Sing BS

Abstract
Objective: To examine BRCA1 and BRCA2 gene sequence testing results, specifically variants of uncertain clinical significance in the BRCA1 and/or BRCA2 sequences of an ethnically diverse population within a particular time constraint. Methods: A retrospective chart analysis of BRCA1 and BRCA2 gene sequence testing cases was reviewed at Kapi‘olani Medical Center for Women and Children from October 1996 to November 2007. Information was extracted and categorized regarding each patient’s age, age of cancer onset, types of cancer in family history, ethnicity/ancestry, type of test used for analysis, and specific characteristics of each variant. Results: Of the 273 patients who received BRCA1/BRCA2 gene sequence testing, 45 patients demonstrated variants of uncertain clinical significance. A total of 48 variants of uncertain clinical significance were reported and 9 of the variants had previously never been observed before. Of the 45 patients, 33.3% were Caucasian, 40% were Asian, and 26.67% were of mixed ethnicity. Conclusions: Within the local population at Kapi‘olani Medical Center for Women and Children, a significantly higher proportion of patients exhibited variants compared to the national average. A high percentage of variants existed among the ethnically diverse as well as the Caucasian population. Gene sequence testing is a valuable asset for physicians treating patients who are at risk for inherited cancer: however, the direction of treatment remains clinically questionable for patients with variants of unknown significance.

Introduction
Epidemiological studies have shown that 5–10% of breast and ovarian cancer cases in the general population can be attributed to heritable cancer-susceptibility genes. These genes, specifically the breast and ovarian cancer genes BRCA1 and BRCA2, encode multifunctional proteins that protect against accumulated DNA damage, the mutant phenotypes of which predispose individuals to both breast and ovarian cancers. BRCA1 is thought to account for the majority of ovarian cancers as well as a high percentage of breast cancers in families in which both early onset breast cancer and ovarian cancer occur. In addition, a second gene, BRCA2, also confers an increased risk of breast and ovarian cancer within high-risk families. Women with mutations in either gene have a predicted lifetime risk of breast cancer between 37–85% and a lifetime risk of ovarian cancer between 15–40%. BRCA1/2 mutation carriers who have already had breast cancer have a 65% risk of developing a second primary breast cancer by 70 years of age. The cancer potential of these genes are not limited to women though, as men have a four-fold increased risk for prostate cancer and a 100-fold increased risk for breast cancer, specifically with the BRCA-2 gene mutation. Identification of these mutations on BRCA1 located on chromosome 17q21, or on BRCA2 located on chromosome 13q12-13, have allowed direct estimates to be made of the risks conferred by these genes. The identification of a patient with Hereditary Breast and Ovarian Cancer Syndrome (HBOS) through a simple blood test and DNA analysis is important, as women who meet clinical or molecular criteria for HBOS are at very high risk for breast and ovarian cancer and this risk can be substantially reduced with clinical intervention.

Current options for patients who have been identified as high-risk for breast cancer include aggressive surveillance, chemoprevention, and prophylactic surgery. It has been reported that a prophylactic mastectomy can lead to a 90–95% reduction in breast cancer among BRCA1 and BRCA2 mutation carriers. Bilateral salpingo-oophorectomy offers similar protection from ovarian and fallopian tube cancers.

Genetic testing is not only becoming widely available, but it is also becoming increasingly important to the clinical management of patients. The BRCA1 and 2 genes are probably the most extensively analyzed breast cancer genes to date. When assessing the clinical significance of a mutation (variant) or change in the normal amino acid sequence of the gene, the following pieces of information must be considered:

1. Type of mutation
2. Location of the mutation within gene (e.g. functional domains, splice sites)
3. Presence or absence and frequency of the variant in a control population
4. Co-segregation or lack of co-segregation of the variant and disease
5. Co-occurrence with a deleterious mutation
6. Type of amino acid change
7. Conservation of the amino acid across species
8. Biochemical/functional analysis
9. Likelihood of cancer in the population with a particular variant

These pieces of information are then used to understand how harmful a particular variant is with respect to the development of cancer. Some DNA changes cause no increase in cancer risk, while others are predictive of certain future cancer. These genes are large and we do not understand the ramifications of every DNA change. Using all the data available allows us to categorize the mutation. Variants are classified as deleterious, conferring a strong risk of cancer; suspected deleterious, uncertain clinical significance; favor polymorphism; or polymorphism/neutral, with no increased risk of cancer. Approximately one third of genetic variants in BRCA1 and half of those in BRCA2 reported in the Breast Cancer Information Core Database (http://research.nhgri.nih.gov/bic/) are categorized as variants of uncertain significance, a designation that can place the patient and clinician in a difficult position with respect to choosing an appropriate clinical treatment option.

Nationally, it is estimated that approximately 5% of patients tested receive a BRCA1/2 uncertain variant test result. Overall, the VUS (Variants of Unknown Significance) rate decreased from 12.8% in 2002 to 5.9% in 2006, a 54% reduction, including decreases of 50.1% for the Western European population, 58.3% for the African population, and 48.6% for the Asian population. From 2006 to 2008, the identification of variants of uncertain significance continued to...
Materials and Methods
Institutional Review Board approval was obtained to review all cases of \textit{BRCA1} and \textit{BRCA2} gene sequence testing offered through Kapi'olani Medical Center for Women and Children from October 1996 to November 2007, ending over a year ago to allow for post-test results to be available. Patients selected for testing had a strong family history of breast or ovarian cancer, cancer themselves at a young age, or more than one type of cancer in the history of the individual.

All initial genetic testing was full sequence analysis unless there was Ashkenazi Jewish heritage or a known familial mutation and was performed at Myriad Genetics Laboratories (Salt Lake City, Utah). Full sequence analysis looks at 22 exons and approximately 750 adjacent intronic base pairs of \textit{BRCA1} as well as 26 exons and approximately 950 adjacent intronic base pairs of \textit{BRCA2}. A number of patients’ DNA samples were also analyzed for five specific \textit{BRCA1} genomic rearrangements (deletions and insertions). If a patient was of Ashkenazi Jewish ancestry, testing for the three common founder mutations was done first, and in some cases was followed by full sequencing if none of the three mutations were detected.

Records were reviewed to determine the number of patients that received genetic counseling, the number of patients that were offered testing, and the number of patients that agreed to be tested. Charts were reviewed and information was abstracted concerning each patient’s age, type of cancer (if any), age of that cancer onset, types of cancer in the family, ethnicity/ancestry, and type of test used for analysis. \textit{BRCA1} and \textit{BRCA2} gene sequence testing results were also reviewed, specifically for variants of uncertain clinical significance in \textit{BRCA1} and/or \textit{BRCA2}. Results were abstracted from the medical record and categorized based on whether the VUS was observed previously, if a family member was subsequently tested for the VUS, the results of their tests, and the type of cancer (if any) in the family member.

Results
There were 572 patients that received genetic counseling through Kapi‘olani Medical Center for Women and Children during the study period. Patients identified as high risk for the presence of a \textit{BRCA1}/2 mutation based on clinical analysis were offered testing. Three-hundred ninety four patients were identified as high risk (365 with a personal or family history of cancer, 26 with Ashkenazi Jewish ancestry and personal or family history of cancer, and 3 men with breast cancer, with or without a family history of cancer). Of the remaining 178 patients, 129 patients were found to be at low or moderate risk for HBOC, and 49 were found to be at risk for another hereditary cancer syndrome. Of the 394 patients who were offered testing, 273 patients agreed to be tested and all received testing. Comprehensive BRACAnalysis® testing, Multisite 3 BRACAnalysis®, and Single Site BRACAnalysis® were the three possible types of analyses that were offered to patients. The Multisite 3 BRACAnalysis® test is a three mutation analysis for individuals of Ashkenazi ancestry, and tests for the specific mutations 187delAG, 5385insC in \textit{BRCA1} and 6174delIT in \textit{BRCA2} found with specifically high frequency in this population. The Single Site BRACAnalysis® is a mutation-specific analysis for individuals with known \textit{BRCA1} and \textit{BRCA2} mutations in their family.

Of the 273 patients who were tested, 75 had a result that was considered positive for a mutation in either \textit{BRCA1} or \textit{BRCA2} and 198 had a result that was considered negative and clinically not significant (196 had Comprehensive BRACAnalysis® of both genes and 3 had Multisite 3 BRACAnalysis® without reflex to full sequencing). Of the 75 patients in whom a mutation was detected, 30 (14 in \textit{BRCA1} and 16 in \textit{BRCA2}) mutations were considered deleterious and clinically significant and 45 were identified as variants of uncertain clinical significance (VUS). Table 1 exhibits the 45 women patients, ages 26-83, with positive results for \textit{BRCA1} and/or \textit{BRCA2} VUS. Of the 45 patients with a positive \textit{BRCA1} and/or \textit{BRCA2} VUS, 39 received Comprehensive BRACAnalysis®, 2 had Multisite 3 BRACAnalysis® followed by Comprehensive BRACAnalysis®, 2 had Comprehensive BRACAnalysis® and Single Site BRACAnalysis®, and 2 had Single Site BRACAnalysis® only. For patients that had additional family members tested, single-site analysis was used to detect the specific VUS that was identified in the first family member tested.

Of the 45 patients, 32 were found to have a single VUS (5 in \textit{BRCA1} and 27 in \textit{BRCA2}). The remaining 13 were further classified into different categories: 3 in \textit{BRCA2} as “favor polymorphism,” 2 in \textit{BRCA2} (both IVS9+G>T) as “suspected deleterious,” 1 had a deleterious mutation in \textit{BRCA2} and 2 VUSs in \textit{BRCA2}, 1 had 2 different VUSs in \textit{BRCA2}, 1 had 3 different VUSs in \textit{BRCA2}, 1 had a VUS in \textit{BRCA1} and a VUS in \textit{BRCA2}, 1 had a “favor polymorphism” VUS in \textit{BRCA1} and 2 different VUSs in \textit{BRCA2}, and 5 in \textit{BRCA2} were subsequently reassigned from a VUS to “normal polymorphism.” A total of 48 variants of uncertain clinical significance were reported. During the study period the VUS identified in 4 patients (one of which had two VUSs in \textit{BRCA2}) were re-classified as normal polymorphisms. The data in Table 1 reflects classifications of the VUSs as of mid 2008.

Of the 45 tested patients, \textit{BRCA2} variants A2351G, G2044V, IVS9+1G>T, M784V, K322Q, and V2739I were seen more than once

<table>
<thead>
<tr>
<th>#</th>
<th>Current Age</th>
<th>Type of Cancer in patient</th>
<th>Age of Onset</th>
<th>Cancer in Family</th>
<th>Ethnicity / Ancestry</th>
<th>Type of Test (Comprehensive, Multi Site, Single Site)</th>
<th>Genetic Test Results</th>
<th>Specific Variant</th>
<th>First Time Variant Seen</th>
<th>Other Family Members Tested</th>
<th>Specific Variant Tested</th>
<th>Variant Test Results</th>
<th>Type of Cancer in Family Member</th>
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</thead>
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<tr>
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</table>

See Table 1 data at http://www.hawaiimedicaljournal.org/carney_m_tab1.pdf
in different patients. The VUSs A2351G, G2044V, IVS9+1G>T were seen in two separate patients, the VUSs K322Q and M784V were seen in three different patients, and the V2739I variant was detected in 5 separate patients. Nine VUSs (4 in **BRCA1** and 5 in **BRCA2**) had previously never been observed before in the Myriad **BRCA1** and **BRCA2** gene sequence testing database. Of the 8 patients who had no personal history of cancer, 2 had a VUS in **BRCA1**, 5 had a VUS in **BRCA2**, and one had a VUS in **BRCA2** that was subsequently reclassified as a normal polymorphism. Of those 8, in 6 cases no other family members were tested, and in the remaining 2 cases a first-degree relative was tested for the same VUS and both had the VUS. In one case, a sister who had no history of cancer was tested and found to carry the same VUS of A1199V. In the same family, a second-degree cousin with breast, ovarian and cervical cancer was tested and did not carry the mutation and was also negative for Comprehensive BRACAnalysis®. In the other case, a mother diagnosed with breast cancer at age 30 received genetic testing at age 44 and was found to carry the VUS of V145del (661del13) (a 50% prior chance). In the two cases that had the IVS9+1G>T VUS in **BRCA2**, family members were tested in both cases. In both cases the sister was tested and only one sister had the VUS and history of breast cancer at age 34 and the other had neither.

The patients were of diverse ethnic backgrounds as illustrated in Table 2. Ethnic classification can be difficult in our population where a large fraction of patients are of mixed ethnicity. Patients were categorized based on their reported ethnicity in conjunction with family pedigree analysis. Table 2 summarizes the categorized racial distribution. Of the 45 patients with a VUS, 18 are Asian only, 14 are Caucasian only, and 1 was Spanish only. The remaining 12 patients are of various ethnic mixes such as Asian/Caucasian, Asian/Pacific Islander, Asian/Caucasian/Pacific Islander, and Caucasian/Pacific Islander with the Asian/Caucasian/Pacific Islander having the highest number of cases of mixed ethnicity.

In 12 families, one or more additional family members underwent Single Site BRACAnalysis® for the specific VUS detected in their family. In one of the 12 families, a second cousin with a personal high risk for HBOS underwent Comprehensive BRACAnalysis® rather than Single Site BRACAnalysis® (Case #22). Several variants were tested for more than one family member. The variants L139P, G602R, A1199V, IVS9+1G>T, F989L and Q147R were each tested in one additional family member for a total of two family members tested (cases #14, 16, 22, 29 and 30). In three cases, a parent and another family member were tested (cases #14, 29 and 30). No parent in these cases had a personal history of cancer and in two cases the additional family member tested did have a personal history of cancer (cases #14 and 30). In case #14, the family members were tested for two VUSs and in the unaffected parent one VUS (G602R) was seen but the other (L139P) was not, and in the affected sister, there was the opposite finding. In case #30, the unaffected father was found to carry both VUSs and the affected aunt did not carry either VUS. In one case, the mother, sister and niece with no personal history of cancer were tested because it was the variant IVS9+1G>T that was designated “suspected deleterious.”

Of the remaining 8 families in which one family member was tested for the VUS, 5 were found to carry the same VUS, 2 were found not to carry the VUS and 1 (case #42), who was tested for three different VUSs was found to carry two (K322Q and M784V) and not the third (S196I). Of the 5 that carry the VUS, three had personal histories of cancer (cases #16, 34, and 45) and two did not (cases #9 and 37). Of the 2 that did not carry a VUS, neither had personal histories of cancer (cases #7 and 31). Case #42 had no personal history of cancer.

**Discussion**

Physicians are remarkably fortunate today to be able to identify patients at risk for inherited cancer syndromes, to test for the mutation in the gene causing this cancer in the pedigree, and to act medically to prevent the cancer from occurring. This paper is the first to describe a hereditary cancer population with such diversity. Nearly 90% of all patients ever tested for the **BRCA1** and 2 mutations are Caucasian: however, this paper describes a population two-thirds of which is considered a minority in this country. Not surprisingly, the study found a large proportion of patients tested with results indicating a variant of undetermined significance. Of all patients who did not have a negative test, that is deleterious mutations and VUS together, 60% were VUS, representing a significantly larger proportion than other nationally published data. Almost certainly, this is because fewer patients tested nationally are of Asian, Pacific Islander, or mixed ethnicity, and VUSs seen in these populations have not been seen with enough frequency to declare accurate clinical significance.

This is of particular concern because physicians truly do not know how to clinically proceed with these indeterminate test results. Should physicians monitor, offer prophylactic surgery, or prescribe risk-reducing medications? Fortunately, as more patients are identified with these variants and their family pedigrees are analyzed for variant associated cancers, many are subsequently classified as

<table>
<thead>
<tr>
<th># of Patients</th>
<th>Ethnic Background Details</th>
<th>Percentage out of Total Patients</th>
<th>Out of 45 Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Caucasian only</td>
<td>26.70%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ashkenazi Jewish</td>
<td>4.40%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Spanish only</td>
<td>2.20%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Total of Caucasian Ethnicity</td>
<td>33.30%</td>
<td>Out of 45 Total Patients</td>
</tr>
<tr>
<td>1</td>
<td>Japanese/Korean</td>
<td>2.20%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Chinese only</td>
<td>8.90%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Japanese only</td>
<td>13.30%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Okinawan only</td>
<td>6.70%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Filipino only</td>
<td>6.70%</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Total of Asian Ethnicity</td>
<td>40.00%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Total of Mixed Ethnicity</td>
<td>26.67%</td>
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</tbody>
</table>
normal variants requiring no additional clinical intervention. Those that are found to have deleterious mutations can have appropriate life saving interventions, preventing almost certain future development of cancer.

Not all patients who need genetic testing receive it, and those who are seen and are recommended for testing are often unable to get it. Many factors account for these realities. The Comprehensive BRACAnalysis® is over $3,000 and many underinsured patients simply cannot afford it. Of the 121 patients who were recommended for testing but were not tested, 41 had either no insurance, denied coverage because their medical history did not meet the insurance company’s defined criteria and the patient was unable to pay for the testing, or the insurance company approved testing but the co-payment (10-50%) was too great. Interestingly, possibly due to similar concerns, 46 of the 121 patients refused to undergo testing.

An even larger issue is providing patients access to basic information, genetic counseling, and genetic testing. In Hawaii, it is estimated that only 20% of patients who should be offered testing have had that opportunity. Dozens of breast and ovarian cancers could be prevented each year in Hawaii if BRCA1 and BRCA2 mutations were identified and prophylactic measures were instituted.

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References

Nalu: ocean wave, surf, to “go-with-the-flow”
John A. Burns School of Medicine (JABSOM) Class of 2014, Profile

Satoru Izutsu PhD, Vice-Dean and Director of Admissions; and Marilyn M. Nishiki, Registrar;
John A. Burns School of Medicine, University of Hawai’i

Dr. Glenn A. Rediger,1 recipient of the 2010 Leonard Tow Humanism in Medicine Award at JABSOM and keynote speaker at the White Coat Ceremony on July 16, 2010, concluded his address to the in-coming class with the following:

“Much is in flux in the practice of medicine, for good or for ill. You may have already sensed some grouchiness and cynicism in some of us old folks caught up in change. Don’t let it infect you. I suppose it is banal to say that you who don white coats today, will shape the profession for the next generation. It is nonetheless true. I have already had the privilege of meeting many of you. I have heard you talk about your experiences, your motivations, your aspirations. I am impressed. It makes me optimistic for the future of the medicine. Keep your focus, keep your faith. And in 25 years or so, when one of you is standing here in my place, the profession of medicine will be stronger and more trusted than it is now, and it will all be for the benefit of the sick. Welcome to the profession of medicine.”

With those words, 33 women and 31 men began working towards their goal of becoming physicians. The class of 64 (increased by two compared to previous years), were selected from a total of 1668 applicants of whom 1434 were non-residents and 234 were Hawai’i residents. Two hundred fifty-one, 79 non-residents and 172 residents, qualified to be interviewed.

The final class of 64 first year students consisted of 58 residents of Hawai’i and six non-residents from throughout the mainland United States and Canada. Residency, for application purposes, was determined by examining six issues: legal resident, birthplace, parent’s legal residence, high school attended, professional or college degree, and legacy (a dependent of an alumna/numus or a faculty member who has at least a 50% appointment in JABSOM). To be considered a resident of the State of Hawai’i for application purposes, a candidate must have had three of the six criteria.

JABSOM continues to describe itself as the most ethnically diverse student body among all medical schools in the United States. Self identified ethnic origins were: Japanese, Other, 11; Chinese, Other, 9; White, 9; Filipino, Other 7; Mixed Asian, 6; Korean, 4; Native Hawaiian, Other, 3; Vietnamese, 3; Asian Indian, 2; Decline to Respond, 2; Guamanian or Chamorro, 2; American Indian or Alaskan Native, Chinese, White, 1; Chinese, Burmese, 1; Guamanian or Chamorro, Iranian, White, 1; Laotian, White, 1; Native Hawaiian, Filipino, Other, 1; Vietnamese, Filipino, White, 1.

Forty-seven were new applicants. There were 9 reapplicants; 7 from Imi Ho’ola (Post Baccalaureate Program at JABSOM) and one delayed matriculant. Ages ranged from 21-31 years, with a median of 23. Fifty-four attended Hawai’i high schools—36 private and 18 public. Four attended mainland high schools, 3 came from high schools in the Pacific Basin, and 3 from foreign schools.

All applicants accepted have a Bachelor of Arts or Bachelor of Science. In addition, 14 have Masters and a doctorate in pharmacy. Forty-one graduated from colleges on the US mainland; 18 from the University of Hawai’i; two from the University of Hawai’i, Hilo; two from the University of Guam; and one from the University of Ottawa. The universities on the mainland United States represented were: University of California-Berkeley, University of California-Irvine, University of Pennsylvania, Pacific University, Scripps College, Stanford University, University of California-Davis, University of Notre Dame, University of Southern California, University of Washington, Boston College, Boston University, Calvin College, Claremont McKenna College, Columbia University, Cornell University, Gonzaga University, Grinnell College, Loyola Marymount, Massachusetts Institute of Technology, New York University, Northwestern University, Simpson University, University of California-Los Angeles, University of Colorado at Boulder, University of Illinois at Chicago, University of Puget Sound, and Yale University.

Undergraduate majors included: 23 Biology, other; 5 Biochemistry, other; 3 Molecular, Cell & Developmental Biology, other; 2 each in Exercise Science, Other; Human Biology; Microbiology, Other; Nursing; Psychology, Other; and one each in Applied Mathematics; Architecture Studies and Urban Design; Biomed Engineer/Physiology; Biological Basis of Behavior; Biomedical Engineering; Botany; Chemistry; Computer Science; Economics; Electrical Engineering; Film/TV and Theater/PreMedical, Epidemiology; Foreign Language/Int’l Affairs/Physiology; Genetics & Plant Biology/Near Eastern Language & Lit.; History of Science-Medicine; History/Social Science; Human Nutrition; Mechanical Engineering; Mol. Cell & Develop. Bio/ Early Chhd Spec. Ed.; Neuroscience; Nutrition; Philosophy; Pre-Prof/Religion, Anat. Biocem and Physio; and, Zoology.

The academic credentials for the entire entering class were: Median Cumulative Grade Point Average (GPA), 3.63; and, median Science GPA, 3.58. Medical College Admissions Test (MCAT) median scores were: Verbal Reasoning-10; Physical Sciences-10; Writing Sample-P; and, Biological Sciences-10. Median Total Score was: 30P.

The process of gaining admission into JABSOM is similar to that practiced by 133 US medical schools accredited by the Liaison Committee on Medical Education of the American Association of Medical Colleges. All applicants must take the Medical College Admissions Test (MCAT) and apply through the American Medical College Admissions Service (AMCAS). This Service compiles transcripts, academic data, personal histories, and letters of recommendations that are sent to the medical schools designated by the applicants.

All applicants who pass an academic screen meet with two assigned interviewers and at the end, the Vice Dean who chaired the
Admissions Committee. The interviewers (faculty, regular and clinical, and fourth year medical students) were interested in learning about the applicant as a person. Therefore, MCAT and GPA scores are not transmitted to the interviewers. Interviewers receive three essays written by the applicants: the “Personal Comments” for AMCAS and two for JABSOM that: 1) “Describe succinctly the important experience(s) in your life which began the process that motivated you to enter the career of medicine” and 2) “Please explain why you are applying to the University of Hawai‘i: John A. Burns School of Medicine.” The interviewers are interested in assessing an applicant’s leadership skills, interpersonal skills, quality of compassion to help people, and stamina and motivation to pursue at least eight years of training and education. The meeting with the Chair of the Admissions Committee ensured that all questions and issues related to admissions were answered in a timely, accurate manner.

There were 11 members on the Admissions Committee: 6 clinicians, 2 basic scientists, 2 clinicians who are also basic scientists, and 1 psychologist. There were 6 men and 5 women who represented the major ethnic groups in Hawai‘i and the various age levels. The committee convened 18 times, beginning in September and ending in March. The activities of the Committee were as follows: a few days prior to a meeting, the completed dossier of the applicant to be discussed was assigned randomly to a member of the Committee. The member went “online” with a designated password to examine the applicant’s folder that consists of: MCAT scores, academic transcripts, and the personal history statement. In addition, the members reviewed the applicant’s interview reports, letters of recommendation, and the applicant’s JABSOM essays. The selected committee member, at the meeting, followed a pre-determined sequence in reporting the highlights of each section of the dossier. Queries about the applicant being presented came from members of the Admission Committee. When the Chair of the Admissions Committee determined that there was an understanding of the “whom” and “what” of the candidate, he called for the casting of a secret ballot. An individual, confidential ballot was submitted by rating the candidate from 1-10. The ratings were not discussed, and submitted to the Registrar (Marilyn Nishiki) who averaged the ratings. These ratings were ranked when all applicants had been evaluated. Fifty-seven were notified of acceptances. The “wait list” was determined by the first natural “cut-off” of the rank order. Seven successfully completed the Imi Ho‘ola (post baccalaureate) Program and joined the incoming class.

Considered each year is ten percent of the class, or six, Out-of-State candidates. These six applicants are those non-residents who have risen to the top 58. All non-residents were separated from the top 58 with their correspondent ratings. The top six were selected, followed by a waiting list. In an entering first-year class, there are generally 58 who are “residents” and 6 who are from out-of-state.

Sixty-four competent, eager, academically prepared men and women began their journey on July 13, 2009 to become the best prepared physicians who will serve human kind in the years to come. The faculty and staff are prepared to fulfill their commitment and contributions to this endeavor.

1. Associate Professor, Department of Medicine, John A. Burns School of Medicine, University of Hawai‘i.

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“Sun Safe Kids,” Implementing a Low Cost, School-based Public Policy to Protect Hawai’i’s Children from Skin Cancer Risks

Kevin D. Cassel MPH, DrPH (c), John A. Burns School of Medicine, Department of Public Health Studies, and Cancer Research Center of Hawai’i, University of Hawai’i

Abstract

The rates of melanomas and skin cancers are increasing in the United States. Children attending elementary schools are in the most danger of acquiring these diseases later in life, and elementary school children in Hawai’i have the greatest risk of all children in the United States. The parents and educators of Hawai’i’s elementary school age children are unaware of the potential risks for cancer that young children experience every day at school. Effective sun protection policies have been implemented in other jurisdictions, including Australia, that have similar risks for over-exposure to solar ultraviolet radiation in children. These proven policy models can inform sun protection practices in Hawai’i. A simple policy whereby public elementary schools require that children wear ordinary long sleeves shirts and hats during the school’s outdoor activities will protect Hawai’i’s children from overexposure to sun’s ultraviolet radiation. Establishment of a state law codifying the implementation of this simple, yet scientifically proven strategy into the policies of Hawai’i’s public elementary schools can significantly reduce the incidence and deaths from melanoma and skin cancer in the state.

The rates of melanomas and skin cancers are increasing in the United States. Children attending elementary schools are in the most danger of acquiring these diseases later in life, and elementary school children in Hawai’i have the greatest risk of all children in the United States. The parents and educators of Hawai’i’s elementary school age children are unaware of the potential risks for cancer that young children experience every day at school. Public elementary schools can simply require that elementary school age children wear ordinary long sleeves shirts and hats during the school’s outdoor activities, applying a “No Hat, No Shirt, No Play” school uniform requirement policy, to protect these children from overexposure to sun’s ultraviolet radiation. Establishment of a state law codifying the implementation of this simple, yet scientifically proven strategy into the policies of Hawai’i’s public elementary schools can significantly reduce the incidence and deaths from melanoma and skin cancer in the state.

Skin cancers are the most preventable type of cancer. Over the past 10 years, the number of deaths from most other types of cancer in the United States, and Hawai’i have dropped significantly. A large portion of this reduction in cancer death rates is attributed to improved primary prevention practices. However, despite improvements in the management of other cancer types, the incidence and death rates from melanoma and skin cancers continue to rise at an alarming rate. There were an estimated 1.4 million new cases of skin cancer diagnosed in the United States, in 2008, accounting for nearly half of all cancer incidence. In Hawai’i, it is estimated that over 5,000 people will be diagnosed and treated for skin cancer this year. The depletion of the earth’s ozone layer, that provides our planet with protection against solar UV radiation, is a major factor contributing to the increasing rates of skin cancer. Hawai’i’s proximity to the equator where the sun rays are more direct, add to this enhanced risk of skin cancer for the local residents and visitors. Efforts to reduce exposure to ultraviolet radiation, particularly in Hawai’i will reduce the burden of this disease.

There are two types of skin cancers, non-melanoma skin cancers, and melanomas. Both are attributable to overexposure to UV radiation, particularly during childhood. Fifty to 80% of a person’s lifetime cumulative exposures to the sun’s UV radiation occur before age 18. Non-melanoma skin cancers, called basal and squamous cell skin cancers occur in the surface layers of the skin. Although these types of skin cancers are often not fatal, they do account for significant morbidity and malaise associated with the excision of a patients’ sun exposed areas, including the skin of the hands, legs, neck, and face. Children who experience severe blistering sunburns are at increased risk for melanomas. Melanomas arise in the skin pigmentation cells, presenting common risks for melanomas in people with dark completions as those with lighter completions. Melanomas are a less common skin cancer type but they are the most deadly type, accounting for 75% of all deaths related to skin cancer.

Parents are legally and morally responsible for the safety and welfare of their young children. Public school teachers, school administrators, and by extension the state governments who manage, fund, and establish policies for public schools, assume this parental responsibility while children attend. In Hawai’i, 97% of children, ages 3 to 14, or about 179,475 students attend elementary schools, and 63% of these students attend public elementary schools in the state. In Hawai’i’s tropical climate, schools are traditionally built with open architectural features and campus layouts to facilitate natural structural cooling by mountain trade winds. These design features of Hawai’i’s schools expose students to direct sunlight while walking between class, during physical education athletic activities, during recesses, and during lunch periods while at school. Hawai’i’s parents and educators unwittingly expose young children to dangerous levels of UV radiation while at school, and establish schools as a primary risk setting for the development of skin cancer in adults. The use of sun protection strategies in elementary school children is estimated to have the potential to reduce the risk of developing skin cancer by 78%.

Educators in both the United States and Hawai’i are receptive and willing to implement sun protection policies for primary school children when the risks are made clear to the school administrators, faculty, and teachers. A study conducted by Buller et al (2002) was designed to assess sun protection policies in the United States. The researchers surveyed 1000 public elementary schools. The study found that only 3.4% of the schools had sun protection policies for children, although 84% reported that the students were outdoors during peak periods of the day for UV exposures. Most of the
administrators, about 72.8%, were willing to adopt sun exposure mitigation policies; however the major reported barriers were lack of awareness of the risks and organizational barriers in school districts. A similar study conducted in Hawai’i by Eakin, et al (2004) found that 99% of the schools in Hawai’i scheduled outdoors activities during the midday peak UV radiation, and that few schools had sun protection uniform policies. Among the primary school educators surveyed in Hawai’i, 78% believed that excessive sun exposure was an important childhood risk for skin cancers, and over a third were in favor of a statewide policy to prevent skin cancer risks in their children.

In the US Center for Disease Control and Prevention’s “Guide to Community Preventive Services” (a compendium of all the empirically tested research on methods to reduce the burden of common diseases in the United States), there are only two interventions recommended to be proven effective methods to prevent skin cancers and melanomas in young people. The first method is the promotion of covering up behavior, including wearing long-sleeved clothing and hats. The second is providing policy changes and education in elementary school settings. These two specific interventions by the CDC are the result of the agency’s systematic review of over 159 studies, considering interventions’ scientific merit, barriers to implementation, overall costs, and cost effectiveness. Several types of prevention strategies were rigorously evaluated to identify the best population-based skin cancer prevention programs. A “No Hat, No Shirt, No Play” policy was recommended as the intervention strategy for primary schools.

The CDC examined studies using various types of interventions, including the development and promotion of public media education campaigns about risk, promoting the use of sunscreen, and enhancing access to and utilization of clinical and self-administered skin cancer screenings. These methods were not found to be as effective, efficacious, or cost-effective as simply having primary school children wear a hat and long sleeves during participation in outdoor activities at school. The development of a “No Hat, No Shirt, No Play” policy in Hawai’i’s public schools offers the application of the best science to prevent skin cancer, and is proven to be an acceptable prevention method for children, their parents, and educators.

There are several examples of school-based policies that have been adopted that can be used as a model to create state legislation for a statewide “No Hat, No Shirt, No Play” policy in Hawai’i’s schools. In the Kidskin study, parental support to enforce their children’s wearing of the program’s recommended “Gold Standard” hat was challenging. The researchers hypothesize that additional parental education may reduce the effect of this parental barrier to the policy. This barrier also underscores the importance of the additional inclusion of adult education about the risks of sun protection in children, combined with the mandatory “No Hat, No Shirt, No Play” policy. These two components can serve to reinforce the adherence to the program.

It is not clear from the Kidskin study whether clothing costs were also a factor associated with preventing parent’s adoption of the “No Hat, No Shirt, No Play” policy. There will be always be parents who are not financially able to meet the “No Hat, No Shirt, No Play” policy program’s requirement to provide a long sleeve shirt and hat for their child. A support program for parents who are unable to provide these apparel resources could be established, and based upon parental income eligibility requirements. Income data from the Hawai’i Department of Business Economic Development and Tourism can be used to determine the cost of such a program. It is estimated that there are about 13% of individuals with children under the age of 18, or about 38,000 people who have incomes that are below state poverty levels. Applying this data, it is estimated that approximately 5,000 children in Hawai’i would need financial support to meet the requirements of a statewide “No Hat, No Shirt, No Play” policy program.

The adoption of a support program for low income families to adhere to a Hawai’i primary school “No Hat, No Shirt, No Play” policy may not require the use of any public funding. As part of the state’s, “No Hat, No Shirt, No Play” policy program, an information list of preferred hat and long sleeve shirt vendors could be included as a resource for parents to obtain the suitable clothing needed to meet the program’s requirements. Clothing vendors, as a benefit for being placed on this vendor resource list, would agree to donate 10% of their expected sales profits in merchandise, and this merchandise would in turn be made available to parents who are unable to meet the “No Hat, No Shirt, No Play” policy program’s uniform requirement for their children.

It is expected that the increased vendor sales revenue realized by requiring parents to include a long sleeve shirt and hat as part of a outdoor school uniform would generate about 3.8 million dollars in new spending if only 85% of the 96,108 public school primary students and their parents adhere to the program by buying shirts and hats at the retail price which will cost about $40.00 (Deputla, personal communication, 2009). Shirt and hat clothing vendors typically make a minimum of about $2 to $4 in profit per item (Deputla, personal communication, 2009). Adding a 10% allocation from vendors would generate about $40,000 in funds towards the support
of the expected 5,000 families needing help. This allocation could still provide the vendors with a minimum of $345,988 in annual net profits to share.

There are additional challenges to the implementation of a “No Hat, No Shirt, No Play” policy in Hawai‘i primary schools. The implementation of this policy, and the requirements for adherence, could dissuade public schools from promoting outdoor activities and seriously curb support of the state’s primary schools already tenuous budgets for athletic programs. The reality of reducing support for primary school physical activity for students could also contribute to the increasing obesity rates in young people. To minimize the potential for the “No Hat, No Shirt, No Play” policy to reduce physical activity in schools, the program can incorporate the use of policy champions. Policy champions could be comprised of prominent athletic figures in Hawai‘i’s culture, including use of University of Hawai‘i sport figures or other well-known local athletes. These champions would serve to extol the benefits of physical activity while simultaneously modeling use of the sun protection apparel used in conjunction with the “No Hat, No Shirt, No Play” policy for schools. Adding the use of these athletic figures or champions is a program component suggested by the Kidskin researchers, and could be part of the program’s educational campaign for schools administrators, parents, and students.

There is a perceived concern by the public, promoted through popular media about the potential for skin cancer prevention strategies to cause a reduced absorption of vitamin D in primary school children, a primary metabolic process enhanced through exposure to sunlight. Researchers in Australia noted that there were public misconceptions arising from these media reports about the benefits of sunlight exposure for the enhancement of natural absorption of vitamin D, Australia’s media reports about vitamin D served to reduce adherence to the established sun protection programs and policies recently developed in this country. This effect was significant despite the lack of empirical evidence that sun prevention activities presented little risk of vitamin D deficiencies in populations. Current research is now being conducted to clarify the role of vitamin D absorption, and identify if there is a relationship between vitamin D consumption and cancer prevention. However, until definitive conclusions are made about the possible harm presented by reduced vitamin D absorption caused by skin cancer prevention programs, there remains a consistent and clear link between skin cancer including melanomas and overexposure to the sun in children. Additionally in the United States most milk and other food products in the United States provide sufficient supplementation of vitamin D for children and adults. The mixed messages about vitamin D deficiencies and sun exposure prevention remain inaccurate and unfounded.

Beyond the subsequent suffering and death in adulthood that will result from failure to implement primary skin cancer prevention policies, there is a great potential for these diseases to present a tremendous and avoidable financial load on Hawai‘i’s healthcare systems. In 1997, the annual cost of treating the estimated 40,000 melanoma cases in the United States was about 567 million dollars, or an average of about $14,000 per patient per year. However, the annual costs per patient are disproportionately spread among the range of patients, with the cost being $1,310 for patients who are diagnosed with early stage disease, versus $42,000 for patients with later stage cancers. These costs do not include indirect costs, incorporating the loss of earnings and other expenses associated with the disease.

The total financial burden of melanoma in the United States is estimated at 1 billion dollars annually. Additionally, these are the costs estimated for the least common type of skin cancer, melanoma. Consider this, cost estimates can be made to include the more common basal and squamous cell skin cancers, and use a treatment-cost model comprised of only excision ($275/pt/yr). Applying this minimum per-person medical cost to the 1.35 million expected new basal and squamous skin cancer cases in the United States, and the 4,950 expected new cases in Hawai‘i, the annual skin cancer treatment costs amount to nearly $39 billion for the United States, and $1,475,000 for Hawai‘i using 1997 dollars. Finally, the incidence of skin cancers and melanomas becomes more prevalent and frequent after age 50, so that this preventable medical and financial burden will most likely be supported through government Medicare disbursements for people who are older.

There are models of effective sun protection policies that have been successfully adopted in Hawai‘i’s private primary schools. Research conducted by a Hawai‘i’s dermatologist, Dr. Nip-Sakamoto at Punahou and Iolani Schools in 2000, pilot tested the efficacy of sun protection education for students, educators, and parents, combined with school policies requiring primary school children to wear sun protection gear including hats (Nip-Sakamoto, personal communication, 2009). Currently, nine years after the initial pilot projects were completed in these schools, both Punahou and Iolani School have instituted broad skin cancer prevention policies that include use of sun protection clothing, education for students, faculty, and parents, and also the new construction and use of sun protective structures in their outdoor sports and recreational facilities (Nip-Sackmoto, personal communication, 2009).

Finally, in Hawai‘i there are models for the legislation that support a requirement for parents to provide disease prevention interventions for their children. Since 2002, State Department of Health’s Administrative Rules support legislation for the “Vax-to-School” program that has successfully demonstrated use of a statewide policy to encourage health promotion in primary school students. The program requires that primary school children, and children in other age groups be administered vaccines for many common diseases including chicken pox, rubella, measles, mumps, hepatitis B, diphtheria, tetanus, and pertussis. This program has supported the vaccination of primary school children through the use of over 260 medical providers. The CDC estimates that the program supports Hawai‘i’s 90% immunization rate for children entering elementary schools. Funding for the program is provided by allocations from the CDC, in conjunction with the Hawai‘i State Medicaid program. The programmatic policy standards of the “Vax to School” program can be successfully adapted for “No Hat, No Shirt, No Play” legislation.

Although there are several barriers that can contribute to the implementation of a mandated statewide “No Hat, No Shirt, No Play” policy for primary school children, there is overwhelming evidence that this type of intervention may be a feasible and an effective method to promote the health and safety of our children. The potential costs of not implementing this simple strategy can be considered using various measures including the potential treatment cost for skin cancer, the personal disfigurements created by these...
treatments, or the number of deaths that will eventually result from overexposure to the sun. Currently there are few options to prevent cancers. There has been great success in changing social norms concerning tobacco use in young people, subsequently reducing mortality rates from this disease. Overexposure to the sun represents the new paradigm in cancer prevention for our children. We can implement changes now that can assure our children a more healthy future.

Disclosure Statement: This policy proposal was developed solely by the author, who has no financial affiliations to disclose at this time.

Conflicts of Interest: The author acknowledges no conflicts of interest associated with the development or publication of this manuscript.

References

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IRRESPONSIBLE CALIFORNIANS LEAD THE NATION IN VACCINE REFUSALS.

As of June fifteenth, 910 cases of pertussis (whooping cough) have been reported and 5 children have died in the state of California, all under the age of six months. An additional 600 cases are under investigation with the likelihood that 2010 will surpass the record of 3,182 recorded in 2005. Although California law provides that all children receive the standard immunizations, for example, polio, diphtheria, pertussis, measles and other infectious diseases before starting school, the law also provides a “personal belief exemption” which need not be based on religious belief nor medical indication. Despite the multiple studies disproving a relationship with social repercussions, and interacting with others behind a locked face might yield a misunderstanding with an angry driver or a customer in a pub.

LEXUS STRUGGLES FOR AUTO-IMMUNITY.

In August 2009 off-duty California Highway Patrol officer Mark Saylor was driving a 2009 Lexus ES 350 lent by a Lexus dealership when the vehicle spontaneously accelerated reaching speeds over 100 miles per hour. A passenger in the car placed a frantic 911 call for help as the car sped beyond control, and could not be stopped by jamming on the brakes. Ultimately the car crashed and caught fire, killing all four occupants. Inspection after the crash found that the floor mat melted on the throttle pedal. Lexus reached a settlement with the families involved but did not reveal the terms of the agreement. Subsequently, Toyota recalled more than eight million autos, mostly to fix floor mats and accelerators. The company was fined $16.4 million, the maximum allowed by the National Highway Traffic Safety Administration (NHSTA) and still faces about 200 lawsuits. NHSTA is still investigating Toyota.

THE BEST LAID PLANS OF MICE AND SENIOR MANAGEMENT.

Avandia (rosiglitazone) was approved by the Food and Drug Administration in 1999 and quickly became a major top-selling drug for GlaxoSmithKline PL with worldwide sales of over $3 billion by 2006. The drug functions to reduce blood sugar in patients with type 2 diabetes, and doctors assumed it would reduce the risk of heart attacks and other complications of diabetes. Doctor Steven Nissen at the Cleveland Clinic published a study in the New England Journal of Medicine (NEJM) in 2007 stating that Avandia actually increased the risk of heart attack. The report was really no surprise to Glaxo since their own studies in 2005 and 2006 showed a 30% increased risk of cardiovascular events and gave that data to the FDA. No action was taken at that time, but now the FDA has restricted Avandia, and European regulators are removing it from the market entirely. The real crime occurred in 1999 when Glaxo’s own research revealed the problem, but senior management in 2001 was quoted in an e-mail “these data should not see the light of day when Glaxo’s own research revealed the problem, but senior management contacted U.S. Treasury Secretary Timothy F. Geithner opposing the policy change. Their letter to Secretary Geithner states the alteration would cost taxpayers $1.5 billion in lost revenue and would act as a financial incentive for trial attorneys to file less meritorious lawsuits against any physician or organization that provides health care. Existing tax rules allow trial lawyers who pay litigation costs upfront for clients to claim tax deductions on those expenses only if there is no award. This proposal is another indication of the immense power of the largest trial lawyer trade group The American Association for Justice. A similar attempt was made last year by Senator Arlen Specter (himself a lawyer) but was defeated. The man in the White House is no friend of medicine.

BEFORE WI-FI AND AMPLIFIERS WE WERE ONLY SUBJECTED TO GHETTO-BLASTERS.

To no one’s surprise who has parked near a vehicle with ear-shattering CD speakers, a study in the Journal of the American Medical Association (JAMA) found that hearing loss in the 12 to 19 age group has increased from 14.9% to 19.5% in the decade ending in 2005. Researchers based the analysis on information gathered from nearly 3,000 children, and suggest that as many as 6.5 million teens in the United States now have some hearing loss. The study was not designed to find the cause of hearing loss, but noise exposure is a known culprit and diet, lack of exercise, and obesity might contribute. Loud music, head-sets and ear buds have become standard for many teens and young adults. Turn on, tune in, and -- huh? What did you say?

ADENDA

Congratulations to long-time HMA contributor Irwin Schatz, M.D. and his family as they watched their son Brian Schatz win the Democratic party nomination for Lt. Governor.

Running is more effective for building bone strength than weight lifting or cycling.

Six percent of American drivers admit to reading while driving.

Procrastinate now. Don’t put it off.

I never believed in casual sex. I always try as hard as I can.

ALOHA AND KEEP THE FAITH — rts ■

(Editorial comment is strictly that of the writer.)
In recent years, hundreds of Hawaii’s physicians have switched their coverage to HAPI, saving thousands of dollars on their medical malpractice coverage costs.

Started 32 years ago, HAPI is Hawaii’s first, physician-owned medical malpractice coverage provider.

As a leading medical malpractice coverage provider, HAPI protects and defends Hawaii’s most influential and respected physicians.

With a strictly local presence and NO profit motive, savings are distributed to our members.

HAPI’s rates have remained stable, with several rate decreases or no change in rates in recent years.

In these tough economic times and challenging industry trends, you don’t have to worry about your medical malpractice coverage costs. Let HAPI’s financially sound, affordable plan protect you. Join your fellow colleagues...contact HAPI and start saving today.

<table>
<thead>
<tr>
<th>Specialties</th>
<th>2009 HAPI’s Total Quarterly Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgery</td>
<td>$4,168</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>$1,373</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>$1,662</td>
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</tbody>
</table>

The above illustration is an example of HAPI’s 2009 fully mature costs. These costs apply to physicians who need three years or more of retroactive coverage upon joining HAPI. If you do not need retroactive coverage or if you join HAPI out of a residency or fellowship, you will pay significantly less than shown above. The above specialties were selected for illustrative purposes only. Call HAPI for your specialty’s costs.

“[What prompted me to search for a new malpractice insurance provider]...was the steep increase in premiums. I am a strong believer that you get what you pay for, but also want value. Malpractice insurance companies should provide good legal support if that fateful day arrives. In addition, I was concerned that certain companies would not have enough reserves to handle large or multiple claims. I checked with the insurance commission and researched the integrity of the attorneys and felt that HAPI has the support that I need at an affordable price. Now, that’s value!”

Lance M. Kurata, M.D., Internist

“[After converting my coverage to HAPI, I was pleased with the cost savings but even more impressed with their immediate attention to my concerns]...It is very reassuring to know that HAPI is highly accessible if there is a concern. I’ve experienced excellent customer service since day one.”

Art Wong, M.D., Pediatrician

“I was pleasantly surprised with the additional savings I received when signing up with HAPI. They have been extremely accommodating in providing liability coverage for my practice, and I would recommend other Osteopathic Physicians to consider HAPI as their carrier as well.”

Leland Dao, D.O., Family Practitioner