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Breast Cancer

Addressing Disparities, Improving Care

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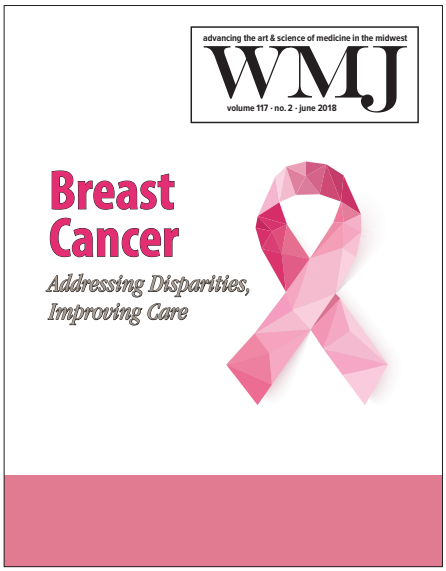

COVER THEME
Breast Cancer: Addressing Disparities, Improving Care

Breast cancer remains the leading cause of new cancer diagnoses among women in the United States and the second leading cause of cancer deaths. This issue of *WMJ* features studies that explore various efforts to affect breast cancer outcomes.

Cover design by Jane Lee

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EDITORIAL

ORIGINAL RESEARCH

REVIEW ARTICLE

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A message from Wisconsin Department of Justice, Brad Schimel, Attorney General, and the Wisconsin Department of Health Services

Wisconsin Department of Health Services

Breast Cancer: Addressing Disparities, Improving Care

Sarina Schrager, MD, MS, *WMJ* Associate Editor

Breast cancer remains the leading cause of new cancer diagnoses among women in the United States and the second leading cause of cancer deaths, behind lung cancer.[1] As with many other chronic diseases, there is a striking racial disparity in breast cancer mortality. And although overall mortality rates from breast cancer in all women have declined over the past 20 years—likely due to expanded screening programs and advances in treatment options—racial disparities continue to exist.

White women and black women have similar rates of new breast cancer diagnoses, yet black women have an approximately 30% higher chance of dying from breast cancer.[1,2] Reasons for this disparity vary. Black women may have multiple barriers to care including lack of health insurance and poor access to mammography screening programs. In some cities, the quality of care may be erratic based on location. When diagnosed with breast cancer, black women are more likely to have a more advanced stage of disease as well as triple negative breast cancer (estrogen receptor, progesterone receptor, and HER2 receptor negative), which is harder to treat and carries a poorer prognosis.[2] All of these factors can impact survival.

Several interventions have been tried to decrease these disparities. Notably, the Metropolitan Chicago Breast Cancer Task Force, which was created in Chicago in 2008 used a comprehensive public health approach to reduce disparities in the community—previously among the highest in the country. The Task Force found a striking variability in quality of mammogram services in different parts of the city and higher uninsured rates for women of color. As an intervention, they provided free, high quality mammography, partnered with community groups to do education about breast cancer screening and ensured that all women received quality care.[3] This multipronged, public health approach reduced the disparity in breast cancer mortality between white and black women by close to half, bringing Chicago in line with data from the rest of the country.

...Although overall mortality rates from breast cancer in all women have declined over the past 20 years—likely due to expanded screening programs and advances in treatment options—racial disparities continue to exist.

The paper by Kamaraju, et al[4] in this issue describes a similar intervention in Milwaukee. The authors partnered with community organizations, presented educational seminars about breast health, and provided information and transportation for women to get free mammograms through the Wisconsin Well Woman Program. They also enlisted a mobile mammography unit that enabled women to get mammography on site at the neighborhood community centers. Over a 2-year period, the project affected almost 500 women and documented significant increases in mammography rates in both women with and without insurance. The Community-Academic partnership employed a community advisory committee and used these community relationships to ensure buy-in from the community groups. In this way, the medical knowledge from the academic partner (Medical College of Wisconsin) was shared with patients in ways that they understood, in an environment where they felt comfortable. This study is a great example of an innovative method to bring health care to the community in order to improve care for underserved women.

Additionally in this issue, 2 studies focus on evidence-based care for women with breast cancer. The project reported by Hill, et al[5] describes an intervention to ensure adherence to national guidelines for women diagnosed with early stage breast cancer. The new guidelines by the National Comprehensive Cancer Network, established in 2016, do not recommend doing screening lab tests in these women. Previously, all women diagnosed with early stage breast cancer routinely had complete blood cell count and liver profile measurements. Using a multipronged intervention that targeted providers and included educa-

tion, feedback, and positive reinforcement (gift cards), the authors successfully achieved over 80% compliance with the new guidelines. This paper is an example of an effective quality improvement initiative.

Teaching residents about quality improvement (QI) is the focus of the paper by Reardon et al.[6] This paper describes the development of a successful QI curriculum for psychiatry residents. The curriculum involves a faculty development component, time to pursue projects, and linking QI projects to Maintenance of Certification within the discipline. Most of the residents who participated completed successful QI projects.

Finally, Chaudhary et al[7] evaluate the predictive power of progesterone receptor status in recurrence rates among women with ductal carcinoma in situ (DCIS). Invasive breast cancers with positive estrogen receptor status but negative progesterone status are more aggressive than those with positive estrogen and progesterone receptor status. The authors evaluated whether that subtype of tumors (estrogen receptor positive and progesterone receptor negative) was predictive of increased rates of recurrence in women with DCIS. They followed a cohort of almost 700 women for 5 years and found that progesterone receptor status did not predict recurrence rates. This information can be helpful when counseling women with DCIS about treatment options.

Breast cancer is common, and women of color continue to experience poorer outcomes after being diagnosed. This issue of the journal summarizes important research from the public health and clinical care perspectives that can help bridge the disparity gap and lead to more equitable outcomes.

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Increasing Mammography Uptake Through Academic-Community Partnerships Targeting Immigrant and Refugee Communities in Milwaukee

Sailaja Kamaraju, MD, MS; Melissa DeNomie, MS; Alexis Visotcky, MS; Anjishnu Banerjee, PhD; Kate Krause, BS; Emmanuel Tavares, BA; Amrita Rao, BS; Elaine Drew, PhD; Joan Neuner, MD, MPH; Melinda Stolley, PhD

ABSTRACT

Introduction: Milwaukee, a city characterized by high rates of racial segregation and a growing immigrant population, has large race-based breast cancer survival disparities. To address these disparities, breast health education workshops were offered through a community-academic partnership (CAP) to women from various ethnic backgrounds. This paper explores attendance, satisfaction, and rates of screening mammography among workshop attendees.

Methods: Partnerships were formed with community-based organizations, a mobile mammography unit, and the Wisconsin Well Woman Program, a state-supported program providing free mammograms. Multilingual staff provided monthly breast health education workshops at community settings and coordinated transportation. Participants completed surveys that included demographics, prior screening history, barriers to screening, and program evaluation. Descriptive statistics were used to summarize and analyze data.

Results: Over a 24-month period, 493 women—most of whom sought services at partnering organizations that serve primarily immigrants, refugees, and racial minorities—attended breast health workshops, with 374 participants completing surveys (mean age = 45 years). A total of 360 were ≥ 40 years old. Among these women, 188 (113 insured [60%], 75 uninsured [40%]) reported no prior mammogram in the past 2 to 5 years. After attending the workshop, mammogram uptake was 100% among the insured and 80% among the uninsured. Satisfaction with the workshops was high; 73% of attendees rated them highly informative.

Conclusions: Our CAP offered culturally tailored breast health education and access to screening via a mobile unit that was well attended, highly rated, and increased screening mammography.

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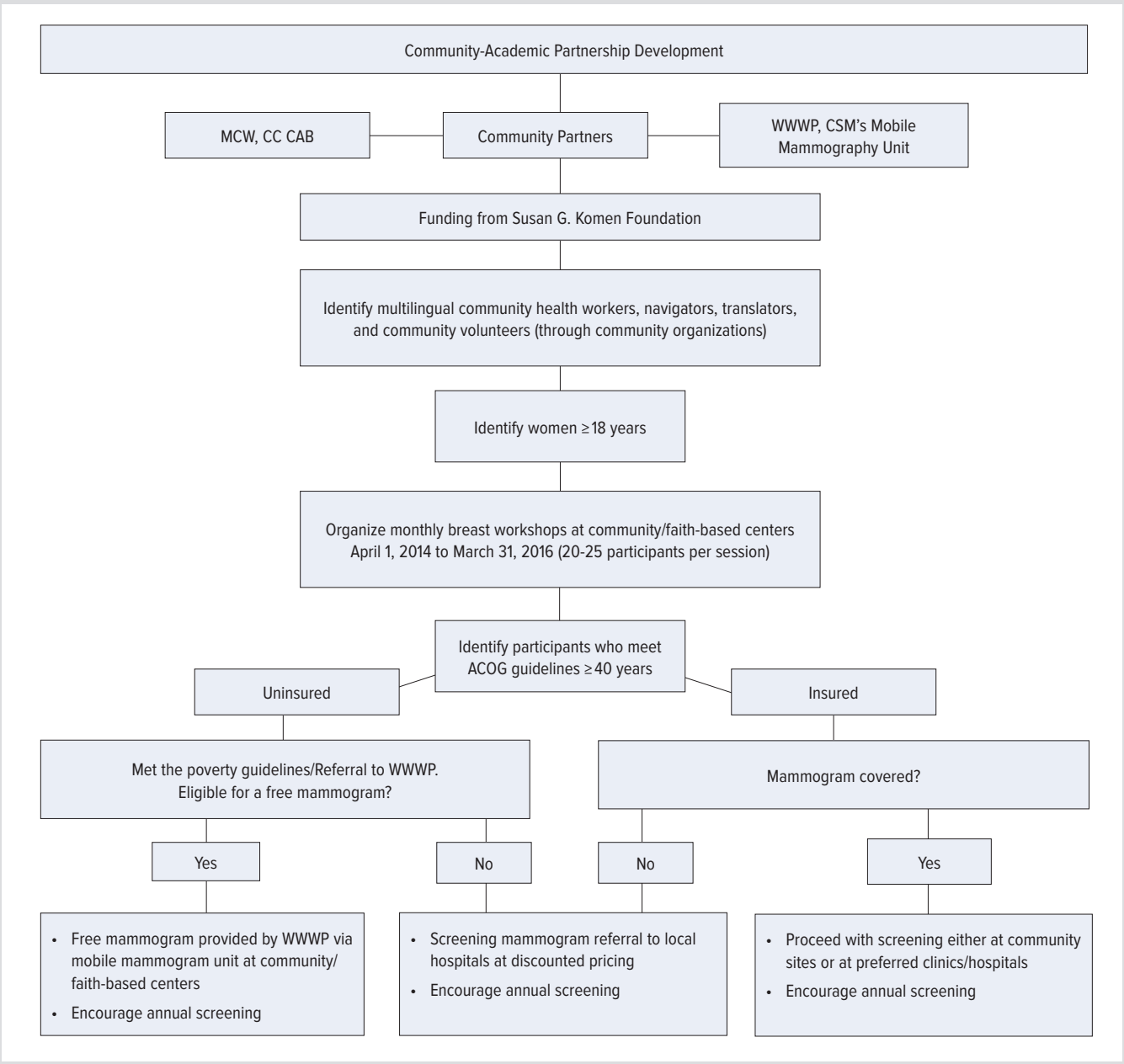
CME available. See page 61 for more information.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women in the United States and the second leading cause of cancer mortality.[1] Regular screening is the key to timely diagnosis and treatment.[2] This can be challenging in populations with cultural, educational, and language barriers, which often exist in tandem with limited access to care.[3-5] African American, Latino, Native American, and immigrant communities demonstrate lower adherence to screening mammograms compared to white populations.[6,7] Factors that preclude women from seeking preventive health measures include lack of awareness, limited English proficiency, transportation barriers, personal beliefs, fear of illness, financial concerns, and work schedules that leave little time for daytime clinic appointments.[8] Methods to identify these impeding factors and efforts to deliver appropriate preventive care through community engagement and outreach are critical to overcome these barriers.[9]

A variety of interventions demonstrate success with increasing screening mammography rates among women facing race-based health disparities. These include patient navigation to improve access and/or reduce practical barriers, community health worker-guided programs to promote education, and events offering mobile mammography.[10] Few interventions include culturally tailored education, navigation, and access to mobile mammography—essential components that support screening—in one easily accessed community setting.[11] Such efforts are challenging and highlight the growing need for multisector partnerships and care delivery models that address the needs of underserved women.

Figure. Project Outline



Abbreviations: MCW, Medical College of Wisconsin; CC CAB, Cancer Center's Community Advisory Board; WWWP, Wisconsin Well Woman Program; CSM, Columbia St. Mary's; ACOG, American College of Obstetricians and Gynecologists.

Community-academic partnerships (CAPs) are an effective way of engaging communities in cancer awareness efforts. Academic partners provide technical knowledge, health care resources, and training to lay navigators and community health workers.[12] Community partners provide cultural expertise, local knowledge, and established relationships with community members. These partnerships can enable the development and implementation of comprehensive and culturally relevant efforts to increase breast health knowledge and promote timely screening among underserved communities.[12-14] Ultimately, such efforts may contribute to a decrease in race-based breast cancer survival disparities.

Recent reports document significant disparities in breast cancer mortality and survival among Wisconsin's African American and Hispanic women compared to white women.[3,15] Breast cancer-specific mortality was higher among the African American (Hazard Ratio [HR] 1.55, $P<0.05$) and Hispanic/Latino population (HR 1.54, $P<0.05$) compared to white women.[15] Milwaukee, a city with high racial segregation and race- and ethnicity- based social and health disparities, is currently experiencing an influx of immigrants and refugees, particularly from Burma, Middle Eastern

countries, Eastern Europe (Albania), and Africa (Somalia).[16] Although not yet documented, based on previous data showing low utilization of recommended screening in newly immigrated women, it may be expected that Milwaukee's recent immigrants will experience poor breast cancer outcomes.[17,18]

Given these demographic shifts and observed race-based disparities, we developed a community-academic partnership to implement a comprehensive breast health education and screening program for minority and newly immigrated women. This partnership facilitated breast health workshops to small groups with assistance from community health workers and translators and use of a mobile mammographic vehicle to provide easy access to screening mammograms. Program effectiveness was measured using a session evaluation. This paper presents the development of the community-academic partnerships and the effects of the breast health workshops on mammography uptake among program participants.

METHODS

Community-Academic Partnership

The Medical College of Wisconsin (MCW) Cancer Center has developed a powerful Cancer Center Community Advisory Board that engages diverse stakeholders, including representatives from minority communities that face race-based health disparities. The advisory board aims to reduce barriers to cancer education, screening, diagnosis, treatment, access, and outcomes in southeastern Wisconsin. Although it focuses on several commonly represented cancers, breast cancer was chosen as the focus for this project because, among women in the United States, breast cancer it is the most commonly diagnosed cancer and the second-highest cause of mortality.[1]

The study investigators are active members of the community advisory board with a history of community engagement and research among African American, Native American, and Latino groups; and the primary investigator has been actively involved for several years in outreach efforts with local African American, immigrant, and refugee community centers. Figure 1 depicts the project outline. Investigators partnered with Southeastern Wisconsin-based community and faith-based organizations that demonstrated an interest in, and commitment to, minority health and health access, breast cancer disparities, and/or women's health concerns. These organizations included the Muslim Community Health Center, African American Center (Islamic Da'wa Center), the Sikh and Hindu temples of Wisconsin, Wisconsin Shirdi Sai temple, and the Albanian, Turkish, Burmese, and Somali refugee communities. Other partners included an academic health care system (MCW), the Wisconsin Well Woman Program, and Columbia St. Mary's—a local health system that provided a mobile mammographic unit (Figure 1). Research oversight was provided by MCW's Institutional Internal Review Board.

Population/ Recruitment

Recruitment for the 1-session breast health education workshops was conducted via flyers posted at participating community centers and ethnic grocery stores, emails, and social media. Flyers were created by the community partners in English and translated to pertinent languages. Interested participants contacted project staff and reviewed study procedures. Eligibility criteria required that participants be women aged 18 and over. Community health workers and volunteers functioned as project liaisons.

Intervention

Breast Health Workshops – The Breast Health Education workshops were offered at a community location monthly from April 1, 2014 to March 31, 2016. They lasted 2 to 3 hours and were attended by approximately 20 to 25 women per session. Additionally, one-on-one sessions were held on several occasions for participants who needed additional assistance with translation. Upon arrival, women were asked to complete an anonymous survey that included questions about demographic information, prior mammographic history, and barriers that prevented them from obtaining mammograms. Survey items were based on previously published studies and refined with feedback from community leaders.[19] Educational material in English and other languages (Arabic, Burmese, Farsi, Hebrew, Hindi, Somali, Swahili, and Urdu) developed by the Susan G. Komen Foundation was provided for later review. Following the survey, a medical oncologist and community health workers provided a 45-minute presentation in English that provided basic information about breast cancer risk, screening recommendations, and prevention. Translators were hired in advance pertinent to the spoken languages of the participants' group as identified by community health workers.[20] Participants also had the opportunity to receive a free clinical breast exam performed by the medical oncologist, a licensed internist, or a nurse practitioner. Participants completed a session evaluation at the end of the workshop.

Project Staff – The project engaged navigators, community health workers (CHWs), and volunteers from the partnering community centers. These individuals were invaluable in providing feedback and suggesting changes to simplify the presentation to improve its effectiveness among workshop participants. Study investigators relied on CHWs and volunteers fluent in various languages to assist with survey completion. CHWs provided healthy snacks and beverages, and facilitated workshop attendance by offering assistance with transportation and child care.

Mammography – A primary message from the workshops was the importance of regular mammography in early detection and successful treatment of breast cancer. American College of Obstetricians and Gynecologists guidelines were utilized for screening mammography starting at age 40 years.[21] Free mammograms were provided by the Wisconsin Well Woman Program (WWWP), a statewide breast and cervical cancer screening pro-

Table 1. Demographic Characteristics of Study Participants, N = 374

Variables	n (%)
Age	
Mean ± SD	44.99 ± 13.49
Native Language	
Arabic	54 (14.4)
Urdu	63 (16.8)
English	110 (29.4)
Punjabi	44 (11.8)
Missing	103 (27.5)
Residency Status	
Legal resident	136 (36.4)
Citizen	196 (52.4)
Missing	39 (10.4)
Visitor	3 (0.8)
Region of Origin	
African American	39 (10.4)
Middle East (Turkey, Iran, Iraq, Afghanistan)	38 (10.2)
Asia (Burma, India, Pakistan)	126 (33.7)
Refugees from Eastern Europe (Albania, Palestine)	26 (6.95)
Refugees from Africa (Somalia, Nigeria)	13 (3.5)
Missing	132 (35.3)
Do you have a primary care provider?	
No	130 (34.8)
Yes	216 (57.8)
Missing	28 (7.5)
Do you have health insurance?	
No	122 (32.6)
Yes	204 (54.5)
Missing	48 (12.8)
Prior Mammogram History: On average, how often do you have a mammogram?	
Yearly	66 (17.6)
Every 2 to 5 years	55 (14.7)
Every 5 to 10 years	14 (3.7)
Every 10 or more years	7 (1.9)
Never	148 (39.6)
Missing	84 (22.5)

Table 2. Reported Barriers to Obtaining Screening Mammogram

Self-reported Barriers to Screening Among the Breast Workshop Participants	N (%)
I do not have health insurance	91 (24.3)
I do not know where to go or who to call for a mammogram	52 (13.9)
I have no family history of breast cancer, so I don't need mammograms	49 (13.1)
I do not know if my health insurance will cover a mammogram	38 (10.2)
I do not know the benefits of getting mammograms	33 (8.8)
I do not speak English and do not know where I can go to see service providers who speak my language	29 (7.8)
I am afraid of finding out I have breast cancer	29 (7.8)
I want to get mammograms but I forget to schedule them	26 (7.0)
I do not have transportation to the clinic where I would get a mammogram	22 (5.9)

gram that provides cancer screenings and diagnostic/treatment services to low-income Wisconsin residents. Workshop participants aged 45 and older were eligible for free screening mammograms if their gross annual family income was below 250% of the federal poverty level. All other women ≥ 40 years of age who did not meet the WWWP's criteria for free mammograms were referred to local community hospitals for mammography and discounted pricing when eligible. While the study intentionally engaged participation from organizations that serve large numbers of immigrants and refugees, WWWP eligibility requirements limited services to documented US/Wisconsin residents.

A mobile mammography unit provided quarterly mammograms in conjunction with scheduled breast health workshops hosted by community organizations. Participant data was entered into Research Electronic Data Capture (REDCap), a secure web-based database used to collect and store research data. For individuals with normal mammograms, study staff emphasized the importance of ongoing annual screenings, while those who required additional follow-up were navigated to the necessary provider and/or resources. The study's principal investigator and primary providers reviewed screening mammogram reports for any additional evaluation (diagnostic mammogram, ultrasound).

Statistical Methods

We calculated descriptive statistics including means, standard deviations, and proportions, wherever applicable, for all variables of interest. Relevant summary statistics for demographic variables, including grouped summaries for ages, are tabulated. Missing data was included in the analysis and grouped into 1 category wherever appropriate, as in tables with demographics and evaluation summaries. Missingness was likely to be at random, but the type of data available precluded investigation of the nature of missingness, which could therefore be a potential limitation of the analysis.

Statistical analysis was performed in SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 493 women attended one of the breast health education workshops. Of these, we excluded 108 women who declined survey completion and 11 women <18 years of age. The final cohort included 374 women with a mean age of 45 years, the majority of whom were residents of the city of Milwaukee and 2 neighboring counties, Waukesha and Kenosha. Demographic characteristics of the study sample are described in Table 1. Study participants were of various racial and ethnic backgrounds with multiple spoken languages, and most participants were naturalized citizens or legal residents. A total of 34.8% participants lacked primary care providers and 32.6% lacked medical insurance.

A total of 360 participants were ≥ 40 years of age and thus appropriate for mammography. Of these, 188 women had reported not receiving a mammogram in the last 2 to 5 years prior to attending

the breast workshops. Women were unable to recollect the details of their yearly mammogram information. Barriers to obtaining a mammogram varied, with many women reporting multiple barriers (Table 2) including lack of or concerns about insurance coverage, lack of time to attend doctor appointments, uncertainty about where to go or who to call to schedule a mammogram, fear of negative findings, lack of transportation, and lack of English proficiency. Following the workshop, mammography increased in both uninsured and insured participants. Seventy-five of the 188 participants in need of current screening were uninsured and qualified for WWWP support to receive free mammograms. Among these, 60 women (80%) received a screening while others were no-shows (Table 3). The majority of the privately insured women (N=113) received their screening either at their primary providers' facility and few (n=<10) through the mobile mammographic unit at their faith-based community center. Additional diagnostic imaging was suggested for 12 women, all of whom were unremarkable except for 1 patient who was diagnosed of breast cancer and successfully completed treatment. Satisfaction with the breast health education workshops was high with most women reporting that they found it informative, the presentation clear, workshop site and group size comfortable, and project staff helpful (Table 4).

Table 3. Mammographic Assistance Through Community-Academic Partnership Project

Eligible Women (≥40 years) who had not received a mammogram in the last 2-5 years prior to the workshop, N=188	**n (%)**
Privately insured women who obtained mammogram after attending workshop (n=113)	113 (100)
Uninsured women who obtained mammogram after attending workshop (n=75) (WWWP and Mobile Unit assisted)	60 (80)

Abbreviations: WWWP, Wisconsin Well Woman Program.

Table 4. Workshop Evaluation Results

Variables	**Total N=374 (%)**
Overall how informative was this workshop?	
Extremely informative	273 (73.0)
A little bit informative	29 (7.8)
Not informative at all	2 (0.5)
Missing information	70 (18.7)
How would you rate the speaker's presentation and clarity?	
Extremely clear	279 (74.6)
A little bit clear	15 (4.0)
Not clear at all	4 (1.1)
Missing information	76 (20.3)
How comfortable was the atmosphere of the community site that you attended?	
Extremely comfortable	279 (74.6)
A little bit comfortable	16 (4.3)
Not comfortable	2 (0.5)
Missing information	77 (20.6)
What did you think of the group size of this workshop/presentation?	
Just about right	278 (74.3)
Too large	7 (1.9)
Too small	13 (3.5)
Missing information	76 (20.3)
How friendly and helpful was our group before, during and after today's workshop?	
Extremely friendly/helpful	280 (74.9)
A little bit friendly/helpful	9 (2.4)
Not at all	1 (0.3)
Missing information	84 (22.5)

DISCUSSION

Our pilot initiative demonstrates the effectiveness of a culturally tailored community-academic partnership in facilitating the delivery of a comprehensive breast health education and screening program for culturally diverse women of southeastern Wisconsin. Despite the ethnic diversity of our sample, participants expressed similar concerns and perceptions regarding screening mammography including access, transportation challenges, busy schedules, fear of disease, and difficulties in language proficiency and scheduling a mammogram. Breast health education workshops, navigation, and access to screening provided at trusted faith- or community-based organizations by culturally and linguistically relevant community health workers contributed to increased mammography uptake in both insured and uninsured women.

Mobile mammography was critical to improving access to screening among participants. Other studies support the value of this resource, citing high rates of attendance by women lacking insurance and/or nonadherent to screening guidelines.[22,23] Lee Yu-Mei et al reported greater preference for mobile mammography (21.3%) compared to hospital-based mammography (7.6%) among women surveyed.[24] A further advantage of mobile mammography is the data showing that mobile mammography may also support repeat visits, promoting adherence to recommended screening guidelines.[25]

Mammography was a top priority for this intervention; however, education, clinical breast examinations, and culturally appropriate support were seen as pathways to promoting future screening adherence. Our breast health education workshops targeted underserved women from minority, immigrant, and refugee communities. Attendance was facilitated by offering the workshops in partnering community- or faith-based settings. In addition, trusted and culturally acceptable navigators and community health workers served as liaisons to assist women in overcoming barriers to attendance such as fear of spousal disapproval, language barriers, and transportation difficulties. Translators also played a key role in facilitating women's participation. Overall satisfaction was high and participants valued the group learning opportunity. Many women highlighted particular aspects of the workshop that they valued most. For example, some participants appreciated hav-

ing access to a health education program that allowed for interaction with academic faculty, while other participants reported that having a clinical breast examination for the first time was most meaningful. Several of the Burmese and Somali refugees shared being totally unaware of breast health, having never attended any health-related educational sessions or events, and thus were especially satisfied with the breadth and depth of information, services, and support.

In addition to facilitating initial workshops and screening access, our community-academic partnership is playing a key role in sustaining these efforts. Participating organizations continue to provide messaging around the importance of breast health knowledge and adherence to regular screening recommendations on an ongoing basis. A local homeless shelter began to include breast health information in its campaign addressing other health issues such as obesity, hypertension, and diabetes through the free medical clinics. Finally, and importantly, following this project, community- and faith-based organizations, in collaboration with academic faculty, received independent funding to support further breast health education; this demonstrates an increased desire and capacity to continue efforts aimed at improving breast health knowledge and screening.

The community-academic partnership was critical to program effectiveness. Each partnering organization played a unique role in ensuring that the project provided essential breast health education and screening in a culturally appropriate setting. This, and other similar projects, can contribute to improved screening adherence and education within communities that face shifting demographics due to immigration and/or an influx of refugees. Traditional screening models rely on patients/community members to seek care at clinical sites, which might be challenging to reach due to transportation challenges or lack of familiarity with the geography of a community; once there, diverse populations might be intimidated by the clinical setting, have language barriers that prevent them from easily navigating the facility, or might face any number of barriers due to their lack of familiarity with the dominant American English-speaking culture.[5] In developing the culturally tailored breast health screening and education project, project partners were intentional about eliminating barriers to improve the education/screening experience for the diverse populations of women being served. Session evaluations – along with feedback collected from attendees – confirmed that the workshops were well-received by attendees. Other projects might consider using these workshops, which combined the clinical expertise of an oncologist with the cultural expertise of community organizations – as a model for effectively addressing health topics with diverse populations of immigrants and/or refugees.

There are also limitations to our study. First, not being a randomized trial, the study lacks the control group necessary to demonstrate actual differences in study outcomes. Second, though our surveys and questionnaires were developed for individuals with low literacy, we had to exclude 108 of the 493 workshop participants who opted out of completing the survey. Further, our efforts to protect patient confidentiality and privacy prevented us from being able to provide assistance with survey completion, resulting in a fair amount of missing data. Unfortunately, due to the nature of the data collected, imputation or other standard statistical methods for handling missing data were not feasible. Future efforts will integrate methods to improve survey completion rates, including refining the survey items for improved comprehension, and interviewer administration.

CONCLUSIONS

This pilot project illustrates the importance of community-academic partnerships in engaging communities in cancer awareness. Future efforts will consider culturally tailored care delivery models utilizing mobile technology and applications to effectively engage with communities facing barriers and disparities.

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Does Progesterone Receptor Matter in the Risk of Recurrence for Patients With Ductal Carcinoma in Situ?

Lubna N. Chaudhary, MD, MS; Zeeshan Jawa, MD; Ahmad Hanif, MD; Aniko Szabo, PhD; Sailaja Kamaraju, MD; Yee Chung Cheng, MD; Christopher R. Chitambar, MD

ABSTRACT

Background: Local recurrence is a major concern in patients diagnosed with ductal carcinoma in situ (DCIS). In invasive breast cancers, estrogen receptor (ER) (+)/progesterone receptor (PR) (-) subtype is considered more aggressive with poorer prognosis as compared to ER+/PR+ tumors. It is unclear whether this holds true in DCIS.

Methods: Six hundred ninety-three patients diagnosed and treated for DCIS at Froedtert & Medical College of Wisconsin Cancer Center (February 2002 to March 2015) were studied to determine if the recurrence rates were significantly different between ER+/PR- and ER+/PR+ tumors. Recurrence was defined as either noninvasive or invasive ipsilateral, contralateral, or distant disease. Probabilities of recurrences were calculated using Kaplan-Meier estimator. Cox proportional hazards model was used to evaluate the effect of prognostic factors on DCIS recurrence.

Results: Median follow-up was 5.2 years. The 5-year recurrence-free survival (RFS) was 91% (95% CI, 88.2-93.3) while estimated 7-year RFS was 86% (95% CI, 81.9-89.2). Seventy-five patients had a recurrence during their follow-up. Patients with ER-/PR- tumors (n = 118) had a significantly higher risk of recurrence (Hazard Ratio 3.7, 95% CI, 1.9-7.2, $P = 0.0001$) whereas those with ER+/PR- subtype (n = 77) did not have a significant difference in recurrence risk (HR 1.75, 95% CI, 0.92-3.32, $P = 0.085$) when compared to ER+/PR+ tumors (n = 482). No endocrine therapy for ER+ DCIS and lumpectomy alone were also significant predictors of recurrence ($P = 0.0073$ and $P = 0.005$, respectively).

Conclusions: ER+/PR- subtype was not a significant predictor of recurrence in DCIS patients. This finding is in contrast to the recurrence risk seen in invasive breast cancers. Mastectomy and postlumpectomy radiation were associated with improved outcomes as was adjuvant endocrine therapy.

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INTRODUCTION

Ductal carcinoma in situ (DCIS) is a non-invasive breast cancer that encompasses a wide spectrum of diseases ranging from low-grade lesions that are not life threatening to high-grade lesions that may harbor foci of invasive breast cancer.[1-4] Local recurrence is the most common adverse outcome experienced by women receiving treatment for DCIS. Estimates of 5- or 10-year recurrence rates are remarkably variable across studies, ranging from 2.4% to 15% for 5 years to 10% to 24% for 10-year recurrence,[5-9] although the older studies may be overestimating the risk. While the recurrence rates for DCIS have fallen over time with increase in screening detection, better surgical techniques, and use of adjuvant therapies, survival after recurrence has been addressed by only a few studies.[10-13] Solin et al reported on the experience of 42 cases with local recurrence and estimated an actual 5-year breast cancer mortality rate of about 16%.[11] In a multi-institutional cohort, the local recurrence rate was 16.7% (n = 45/268) for women who received treatment for DCIS, while the 15-year cause-specific survival was 96%.[12] More recently, Narod et al reported 20-year breast cancer-specific mortality rate of only 3.3% for a large cohort of women (n = 108,196) diagnosed with DCIS.[13] Younger age, black ethnicity, high tumor grade, and negative estrogen receptor (ER) were significant predictors of breast cancer-specific mortality. Progesterone receptor (PR) status was not assessed in this study. Despite the high survival rates, local recurrence is a serious problem and understanding the risk factors to prevent recurrence is essential.

ER+/PR- are highly relevant biomarkers for invasive breast carcinoma as well as DCIS. Generally ER+/PR+ and ER+/PR- invasive breast cancers are treated similarly and are thought to be hormone-sensitive tumors; however ER+/PR- subtype is now recognized as a distinct biological and clinical entity associated with a worse outcome. In the setting of ER+ breast cancer, studies have shown that the absence of PR is an independent predictor of poor response to endocrine therapy, associated with higher recurrence rates and shorter survival times for invasive disease.[14] However, it is unclear if this holds true in DCIS, and the association between PR status and patient outcomes is not as extensively reviewed.

The aim of this study was to determine the association of PR- status with outcomes (recurrence ie, noninvasive or invasive ipsilateral, contralateral, or distant disease) in DCIS patients with the primary objective to assess if a significant difference exists in the recurrence rates for ER+/PR- tumors when compared to ER+/PR+ tumors.

METHODS

Patient Population and Data Collection

Patients with DCIS diagnosed and treated at the Froedtert & Medical College of Wisconsin Cancer Center from February 2002 to March 2015 were included in our study. In all, 969 patient charts were reviewed, of which 693 were included in this analysis. Charts were not included if they had incomplete patient information and/or single clinic visit with no additional follow-up. Patients with previous history of DCIS or invasive breast cancer were excluded, as were patients with micro invasion or presence of invasive breast cancer on final surgical staging. Data on patient and tumor characteristics were collected. The study was approved by the Institutional Review Board and the Protocol Review and Monitoring Committee of the Medical College of Wisconsin.

Estrogen and progesterone receptors were evaluated by immunohistochemistry (IHC) on formalin-fixed paraffin-embedded tissue using clone 1 D5 for ER and clone PgR 636 for PR (Dako, Carpenteria, CA). In 2008, our institution switched to clone SP1 for ER and clone SP2 for PR (Ventana, Tucson, AZ). Detection utilized a monoclonal polymer. In 2012, the nuclear staining criteria for ER and PR was revised to consider any nuclear staining in 1% or more of the malignant cells to be positive and less than 1% to be considered negative, it being ≥ 10% for positivity prior to 2012.

Statistical Analysis

Descriptive statistics were used to summarize sample characteristics. Probabilities of recurrences were calculated using Kaplan-Meier estimator. Loglog-transformed 95% confidence intervals for recurrence probabilities were calculated. Cox proportional hazards model was used to evaluate the effect of prognostic factors on DCIS recurrence. Multivariate models were built using the forward selection with significance level of 0.05. The primary objective of this study was to assess if a significant difference exists in the recurrence rates for ER+/PR- tumors when compared to ER+/PR+ tumors; therefore the variable for ER/PR status was held in the model at each step. Other variables considered were age at diagnosis, body mass index (BMI), menopausal status, history of oral contraceptive use and/or hormone replacement therapy, tumor size, tumor histology, grade, necrosis, surgery, radiation, and endocrine therapy. Recurrence was defined as either noninvasive or invasive ipsilateral, contralateral, or distant disease. All the *P* values are 2-sided. SAS Studio 9.4 was used to perform all statistical analysis.

Table 1. Patient and Tumor Characteristics

Patient Characteristics	**N (%)**	**Median (range)**
Total number of patients	693	
Median age		53 (21-91)
Median body mass index		27 (17-65)
Postmenopausal	480 (69)	
Oral contraceptive pill use	301 (43)	
Hormone replacement therapy use	201 (29)	
Tumor Characteristics	**N (%)**	**Median (range)**
Median size		0.8 cm (0.2-6.5)
Histology		
Solid	349 (52)	
Cribriform	290 (43)	
Micro papillary/papillary	35 (5)	
Comedo necrosis	423 (61)	
ER/PR status		
ER+/PR+ tumors	482 (71.2)	
ER+/PR- tumors	77 (11.4)	
ER-/PR- tumors	118 (17.4)	
Tumor nuclear grade		
Low	125 (18)	
Intermediate	305 (45)	
High	250 (37)	
Negative surgical margins	671 (97)	
Treatment		
Lumpectomy	517 (75)	
Mastectomy	169 (25)	
Radiation (postlump)	450 (87)	
Endocrine therapy (ER+ pts)	286 (51)	
Patients with recurrence	75 (11)	
Type of recurrence		
In-situ	44 (6)	
Invasive	31 (5)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

RESULTS

Patient Characteristics

Patient and tumor characteristics are summarized in Table 1. Six hundred ninety-three patients were included in our study. Median age at diagnosis was 53 years (range 21-91) and median BMI was 27 (range 17-65). Most women were postmenopausal (69%) and were primi or multiparous (65%). Median tumor size on pathologic evaluation was 0.8 cm. Most of the tumors were intermediate (45%) or high nuclear grade (37%). ER+/PR+ tumors comprised 71.2% of the tumors. Most of the patients underwent

Figure 1. Kaplan-Meier Estimate of Being Recurrence Free in Patients With Ductal Carcinoma in Situ

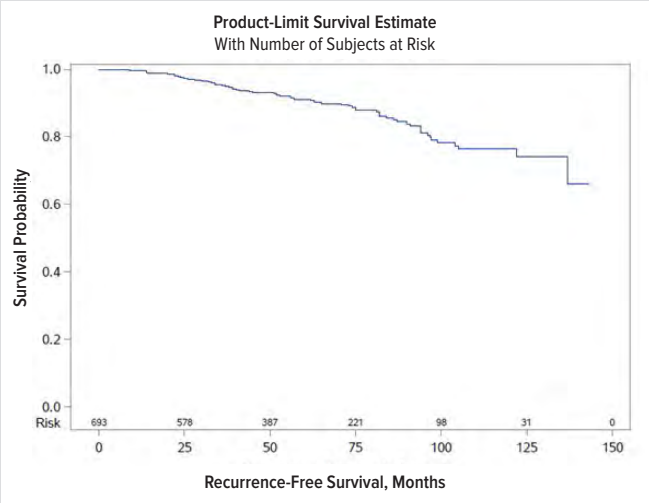
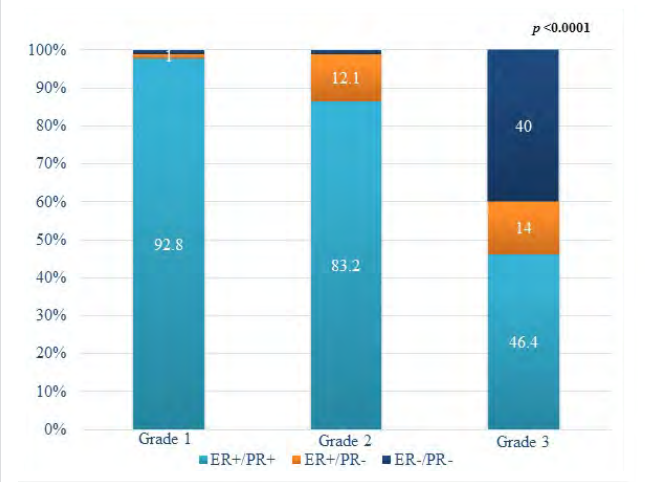


Figure 2. Association of ER/PR Status With DCIS Tumor Grade



Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Results of Multivariate Analysis for Recurrence in DCIS Patients

Variable	HR (95% CI)	*P* Value
ER/PR status		**0.0004**
ER+/PR+	1.00	
ER+/PR-	1.75 (0.92-3.32)	0.085
ER-/PR-	3.7 (1.9-7.2)	**0.0001**
Endocrine Therapy/ER Status		**0.0073**
ER+ with endocrine therapy	1.00	
ER+ without endocrine therapy	2.2 (1.23-3.92)	
Surgery/Radiation		**0.0003**
Lumpectomy+RT	1.00	
Lumpectomy alone	2.5 (1.32-4.93)	**0.005**
Mastectomy	0.34 (0.15-0.8)	**0.014**

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; RT, radiation therapy.

lumpectomy (n=517, 75%) and a large proportion of them received post lumpectomy radiation (n=450, 87%). Endocrine therapy was received by 51% of ER+ patients. It is to be noted that the proportion of patients not receiving endocrine therapy was similar between ER+/PR+ and ER+/PR- cohorts.

Outcomes

Median follow-up was 5.2 years. Five-year recurrence-free survival (RFS) was 91% (95% CI, 88.2-93.3) while 7-year RFS was 86% (95% CI, 81.9-89.2) as shown in Figure 1.

Seventy-five patients were found to have a recurrence during their follow-up. Forty-four patients had DCIS recurrence, 4 of whom had both ipsilateral and contralateral DCIS recurrence. Most of these patients had intermediate or high nuclear grade tumors at their initial DCIS diagnosis (n=16 and n=22, respectively) with only 6 patients having low-grade tumors at diagnosis.

Thirty-one patients had invasive ductal carcinoma (IDC) at recurrence, 3 of whom had distant disease. Assessment of their DCIS tumor grade at diagnosis showed grade 2 and 3 tumors for the majority of these patients (n=13 for grade 2 and n=12 for grade 3). Seven patients had human epidermal growth factor receptor 2 (HER2/neu) positive disease at their invasive recurrence.

ER/PR Status and DCIS Tumor Nuclear Grade

Most of the grade 1 tumors were ER+/PR+ whereas almost all of the ER-/PR- subtype were high-grade tumors. ER+/PR- tumors were mainly intermediate and high grade ($P < 0.0001$) as shown in Figure 2. In our cohort, there were no ER-/PR+ DCIS cases identified.

Multivariate Analysis

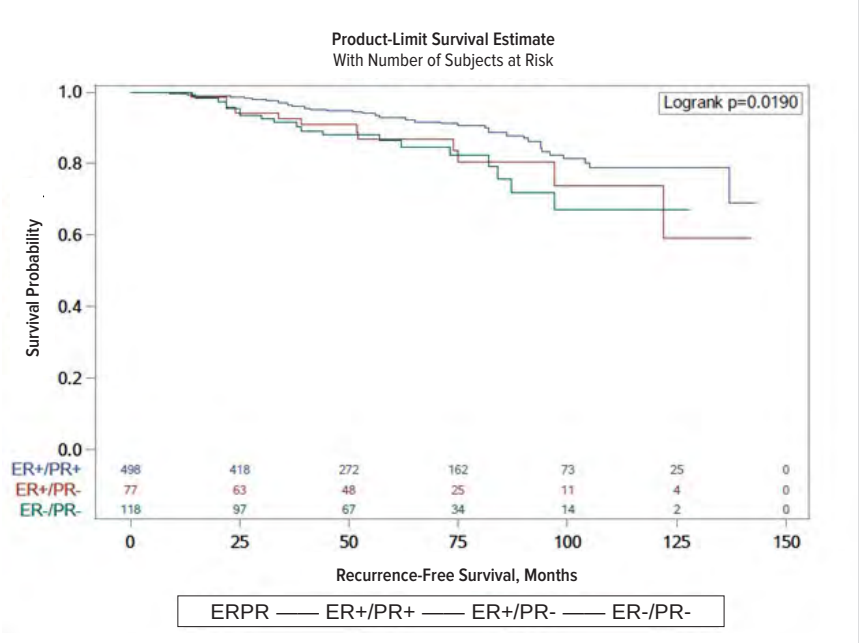
Multivariate analysis showed that among all covariates assessed, ER/PR status, endocrine therapy, surgery, and radiation were found to be significant predictors of recurrence in DCIS patients (Table 2). As compared to ER+/PR+ tumors, patients with ER-/PR- tumors had a significantly higher risk of recurrence ($P = 0.0001$) whereas ER+/PR- tumor subtype did not have a statistically significant difference in risk of recurrence ($P = 0.085$) as shown in Figure 3.

Patients not receiving endocrine therapy for their ER+ DCIS had a significantly higher risk of recurrence as compared to those who received it ($P = 0.0073$). When compared to lumpectomy/radiation, lumpectomy alone had a significantly higher risk of recurrence ($P = 0.005$) whereas mastectomy was associated with a significantly lower risk of recurrence ($P = 0.014$).

Given the significantly lower risk of recurrence after mastectomy, we performed a subgroup analysis of patients without the mastectomy cohort. The recurrence rate was 13.2% among the patients who underwent lumpectomy for their DCIS (n = 68/517). Multivariate analysis of this cohort still showed ER-/PR- status (Hazard Ratio 3.93; 95% CI, 1.96-7.87; $P = 0.0001$), no endocrine therapy within the ER+ cohort (HR 2.4; 95% CI, 1.31-4.41; $P = 0.004$) and not receiving post-

lumpectomy radiation (HR 2.49; 95% CI, 1.29-4.80; $P = 0.006$) to be associated with a significantly higher risk of recurrence. ER+/PR- tumor subtype was not a significant predictor of recurrence (HR 1.39; 95% CI, 0.67-2.8; $P = 0.36$).

Figure 3. Recurrence-Free Estimates by ER/PR Status



Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

DISCUSSION

DCIS of the breast is the most common type of noninvasive breast cancer and is considered a direct precursor for invasive breast cancer.[15,16] Local recurrence denotes a major concern in patients diagnosed with DCIS, as its invasive component—if present—can be associated with high rates of distant disease and mortality.[11,17] Therefore, the need to identify patients at risk for DCIS recurrence, as early and efficiently as possible, appears as a significant priority.

In invasive breast cancers, ER+/PR- subtype is now recognized as a more aggressive tumor phenotype with poorer prognosis as compared to ER+/PR+ tumors.[18] Whether this finding holds true in DCIS is not yet clear. Several studies have assessed the association between hormone receptors and patient outcomes in DCIS with conflicting results. Generally, most of the studies are consistent in their findings that positive ER status is associated with reduced likelihood of local DCIS or invasive recurrence.[19-22] Some of these studies showed a tendency toward less local DCIS or invasive cancer recurrence in PR-positive women.[19,20,23-25]

A nested case control study by Provenzano et al reported a significant risk reduction for local recurrence by 80% (adjusted OR 0.2; 95% CI, 0.1-0.8, $P = 0.02$) for ER+ and 60% (adjusted OR 0.4; 95% CI, 0.2-0.9, $P = 0.03$) for PR+ patients.[20] A recent study by Meattini et al reported 5-year and 10-year local recurrence rates of 4.9% and 10.2%, respectively, in 278 patients with DCIS and a median follow-up of 10.8 years.[22] Inadequate final surgical margins and negative ER status negatively influenced the local recurrence rates.

Our study had a much larger sample size and similarly showed that ER-/PR- tumors were associated with a significantly increased risk of recurrence as compared to ER+/PR+ DCIS. However, ER+/PR- subtype was not a significant predictor of recurrence. This finding is in contrast to the risk of recurrence and tumor aggressiveness seen in invasive breast cancers, which raises the question of tumor biology and carcinogenesis. It is often difficult to differentiate between true recurrence and a second primary carcinoma, especially when it involves the ipsilateral side. There has also been growing interest in HER2/neu status in DCIS and its correlation with tumor aggressiveness and recurrence rates, however the significance of HER2 status in DCIS is not yet clear. We did not have information on HER2 status in our study population as routine testing for HER2 in DCIS is not currently recommended.

Our study also showed significantly higher risk of recurrence for patients undergoing lumpectomy alone as compared to those receiving post-lumpectomy radiation, whereas mastectomy has a significantly lower risk of recurrence. These findings are in agreement with the published literature. Mastectomy provides excellent local control, approximately 90% at 7 years, with an overall recurrence rate of 1.5%.[26] However, it is difficult to justify mastectomy for a pre-invasive condition that should be curable with adequate local excision. There are no randomized trials comparing breast conservation plus radiation with mastectomy in DCIS analogous to the NSABP B-06 trial for invasive breast cancer. The benefit of adjuvant radiation in reducing local recurrence in those undergoing breast conservation has been well established given the long-term data from the NSABP B-17 and NSABP B-24 trials.[27] Recently Sagara et al reported a significant correlation of a patient prognostic score comprised of age, tumor size, and grade with survival benefit from post lumpectomy radiation.[28]

Endocrine therapy has been well established in reducing the risk of local ipsilateral and contralateral recurrence in ER+ DCIS patients. The addition of tamoxifen for 5 years after breast conservation and radiation significantly reduced the risk of recurrent DCIS or invasive carcinoma in the NSABP B-17 and B-24 trials.[6,27] Similar risk reduction was seen in the UK/ANZ DCIS trial in tamoxifen treated patients.[29] Aromatase inhibitors in postmenopausal women with ER+ DCIS also have shown reduc-

tion in breast cancer recurrence risk, with NSABP B-35 showing anastrozole to be superior to tamoxifen[30] whereas the IBIS-II DCIS study reported them to be equivalent.[31] Our study further supports and adds to the current literature by showing that patients who did not receive endocrine therapy for their ER+ DCIS had a significantly higher risk of recurrence as compared to those who received endocrine therapy.

The primary clinical dilemma in the management of DCIS patients relies on the fact that traditional clinicopathological features may not accurately predict disease recurrence in every patient. Great advances have been made in the use of molecular genomic profiling of invasive cancer for risk assessment; however, its implementation in clinical practice for the study of DCIS is lagging behind. The field of DCIS is growing and there are efforts to incorporate detailed genomic and molecular predictors into clinical practice. Recently, a modified form of the Oncotype DX recurrence score for invasive breast cancer (Genomic Health, Redwood City, CA) has been developed for DCIS. The DCIS score may be helpful in facilitating patient-specific recommendations for adjuvant radiation based on the risk of an ipsilateral breast event and recurrence risk. However, it is unclear how this information will fit beyond the decision making for postlumpectomy radiation. Furthermore, incorporating the DCIS score into everyday clinical practice for all patients with DCIS may not be cost effective[32] and needs to be further validated to confirm how much additional prognostic information could be derived from its use. Currently, clinicians and medical oncologists still rely very strongly on tumor biology and molecular subtypes for their clinical decision making and discussion of management and prognosis of such patients.

We acknowledge that our study has a number of limitations. Retrospective design, small sample size, short median follow-up and therefore the small number of recurrences in this study may have decreased the power to detect statistically significant differences.

CONCLUSION

Unlike invasive breast cancer, we did not find the ER+/PR- subtype to be a significant predictor of recurrence in DCIS. However, it is worth mentioning that although the hazard ratio of 1.75 was not significant, the confidence interval (0.92-3.32) is wide and the estimated effect would be important if true. Given the low event rate and the small number of the ER+/PR- group in our study, the effect would have had to be fairly large to be detectable. Although currently the treatment of ER+ DCIS does not differ based on PR status, knowing if PR status is independently prognostic of recurrence would be important for patient counseling, decision on postlumpectomy radiation, and encouraging compliance with endocrine therapy. It would be important to assess this further in larger confirmatory studies that would help elucidate the value of PR expression in recurrence risk determination of DCIS.

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A Strategy for Changing Adherence to National Guidelines for Decreasing Laboratory Testing for Early Breast Cancer Patients

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ABSTRACT

Introduction: Past studies indicate delays in adoption of consensus-based guideline updates. In June 2016, the National Comprehensive Cancer Network changed its guidelines from routine testing to omission of ordering complete blood cell count (CBC) and liver function tests (LFT) in patients with early breast cancer. In response, we developed an implementation strategy to discontinue our historical practice of routine ordering of these tests in asymptomatic patients.

Methods: The ordering of CBC and LFT for clinical stage I-IIIA breast cancer patients was audited in 2016. In June 2016, we utilized the levers of the National Quality Strategy implementation methodology to enact a system-wide change to omit routine ordering. To measure the plan's effectiveness, guideline compliance for ordering was tracked continually.

Results: Of 92 patients with early stage cancer in 2016, the overall rate of compliance with guidelines for ordering a CBC and LFT was 82% (88/107) and 87% (93/107), respectively. Segregated by the pre- and post-guideline change time period, the compliance rates for ordering a CBC and LFT were 78% and 87% ($P = 0.076$).

Conclusion: In contrast to historical reports of delays in adoption of new evidence-based guideline changes, we were able to quickly change provider practice during the transition from routine ordering to omission of ordering screening blood tests in newly diagnosed patients with early breast cancer.

INTRODUCTION

In patients with newly diagnosed breast cancer, routine blood testing to screen for metastatic disease increases cost but does not improve detection.[1] Specifically, ordering complete blood cell count (CBC) and liver function tests (LFT) add a charge but seldom add value to a patient encounter. Recognizing this, the National Comprehensive Cancer Network (Network) updated its breast cancer care guidelines in 2016 to recommend against routine screening blood tests in patients presenting without symptoms.[2] By doing so, its past recommendation was reversed to not order these tests in patients presenting with early clinical stages of breast cancer. As such, the Network aligned itself with multiple other oncology stakeholders to reduce practices of care that were "overutilized."[3-6]

Our breast center previously has demonstrated high in-house compliance with guidelines for diagnostic evaluation and treatment of patients with breast cancer.[7,8] To maintain compliance, our aim with the initiative described herein was to measure compliance with guidelines for ordering CBC and LFT before and after the calendar date when the guidelines transitioned from routine to unnecessary. To aid this effort, we used the levers endorsed by the Agency for Healthcare Research and Quality in its National Quality Strategy to accelerate our rate of adoption of guideline changes.[9,10]

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METHODS

Institutional Review Board approval was obtained from the Gundersen Clinic Human Subjects Committee/Institutional Review Board to review our patient registry and electronic medical records for guideline compliance.

In 2013, Proctor et al—for the purpose of clarity, reproducibility, and testing—proposed guidelines for reporting 7 dimensions of an implementation strategy.[11] Insofar as possible, the description of our implementation strategy is compliant with these recommendations.

Compliance Culture

The study was performed in an interdisciplinary breast center accredited by the National Accreditation Program for Breast Centers. Since 2009, our compliance with guidelines for breast cancer care has been audited during "real time" patient contact by use of an electronic synoptic template embedded within our electronic medical record.[7,8] Trained abstractors entered this data into a patient registry. Furthermore, as patients were presented at tumor board, their providers or other tumor board members described whether their care plan was compliant with guidelines. Deviations prompted discussion. When applicable, guidelines and Consensus Statements, including but not limited to those of the American Society of Clinical Oncology, the Society of Surgical Oncology, the American College of Radiology, the American Society for Therapeutic Radiology and Oncology, and the American Society of Breast Surgeons, were also cited during discussions in real time during an interdisciplinary clinic in which all specialists saw the patient in the same geographic location on the same day. Additionally, one of two breast nurse navigators met with every patient. In doing so, they aided our compliance culture because historically these navigators were up-to-date with recommendations for diagnostic testing and treatment. The navigators were always encouraged to speak up whenever they recognized guideline deviations, including those related to preoperative testing.

Patients and Outcome Measurements

Breast cancer patients with early stage breast cancer [Clinical Stage I, II, and IIIA (T3N1M0)] presenting from January 1, 2016 through December 31, 2016 were identified. Patients were excluded from review if they were diagnosed during June, the month of the change in the guidelines ("washout" period) or if they presented with signs or symptoms suggestive of metastatic disease, stage greater than IIIA, prior history of breast cancer, recurrent breast cancer, or a recent nonbreast cancer diagnosis. Frequency of ordering CBC and LFTs (overall and per provider), subsequent testing prompted by abnormal results, and overall compliance with guidelines were entered into an Excel spreadsheet. If the patient underwent neoadjuvant chemotherapy, then ordering the CBC and LFTs was considered guideline compliant. In order to assess hospital charges and patient cost for laboratory testing, all patient charges were converted to Medicare equivalent dollars.

Institutional Setting

Gundersen is part of a physician-led, not-for-profit integrated health care system serving 19 counties in Wisconsin, Iowa, and Minnesota (estimated population > 500,000). The main facility is a 325-bed regional referral hospital with attached outpatient clinical space, located in a city with a population of about 50,000. The system includes 30 regional clinics and 5 rural hospitals. A comprehensive interdisciplinary breast center is housed on the primary clinic campus, but also provides outreach diagnostic breast imaging at 5 rural sites. Weekly breast cancer tumor boards are held on the main campus and patients under the care of rural surgeons are presented as requested. The system is fully integrated with an electronic medical record that is consistent between the primary hospital and all branch clinics. The medical center supports more than 10 residency training programs and has been designated the Western Academic Campus of the University of Wisconsin (UW) School of Medicine and Public Health. About half of all UW medical students have 1 or more rotations at our institution.

At the main campus, approximately 200 new patients receive a diagnosis of breast cancer each year. During the study period, patient care and "privileges" to order blood tests were provided by 4 fellowship-trained breast radiologists, 6 medical oncologists, 4 radiation oncologists, and 2 surgeons. As part of our institutional policy to comply with the Standards of the National Accreditation Program for Breast Centers, at least 1 representative from all these service lines was required to attend all tumor boards and forward any new guideline or breast center policy change to their respective departments.

Implementation Strategy

The study implementation strategy to change ordering of blood tests utilized the levers of the National Quality Strategy.[9,10] Beginning at the time of changes in the guideline (June 1, 2016), the planned levers included those described below.

This strategy was implemented entirely by the authors without formal involvement by nonmedical quality improvement staff. After study completion, the results were shared with the Quality Department, the Cancer Committee, the National Accreditation Program for Breast Centers site reviewer, and each in-house breast cancer provider of care.

1) Learning and Technical Assistance – PowerPoint presentations were delivered at 2-month intervals beginning June 2016 by a surgical resident-in-training (LH), a medical student (CK), and the principal investigator (JL). During these presentations, changes in breast cancer guidelines for testing were cited. In addition, the general topic of testing appropriateness, as recommended by the American Board of Internal Medicine's Choosing Wisely® campaign, was presented along with examples from the literature as overutilization of testing in breast cancer care.[3-6] Furthermore, a concurrent National Cancer Institute-funded Wisconsin quality initiative that aimed to add value to breast cancer care by decreasing unnecessary testing was discussed.[12] Other presentations were delivered on June 3, 2016 and July 28, 2016. Each of these included measurement and feedback as discussed below. Lastly, the guideline changes for testing were cited during numerous individual patient presentations at weekly tumor boards for

Table. Patient Characteristics Pre- and Post-Change in National Comprehensive Cancer Network Guidelines for Ordering CBC and LFTs

Variable	Pre-Guideline Change n = 40	Post-Guideline Change n = 52	*P* Value
Mean age, years	63.8 ± 15.3	61.9 ± 11.8	0.519
Sex, n (%)			0.999
Female	38 (95)	50 (96)	
Male	2 (5)	2 (4)	
Stage, n (%)			0.071
0	1 (3)	0	
1A	31 (78)	30 (58)	
2A	7 (18)	16 (31)	
2B	1 (3)	6 (12)	

Abbreviations: CBC, complete blood cell count; LFT, liver function test.

3 months following the date of the guideline change. The tumor board audience included but was not limited to physicians, residents/fellows-in-training, medical students, associate providers, and support staff (breast nurse navigators, oncology nurses, medical assistants, and research associates).

2) Measurement and Feedback – After initial implementation of our improvement strategy, an academic researcher (AV) audited the patient's electronic medical record for guideline compliance at both the individual ordering provider level and in the aggregate. With these results, we provided peer performance comparisons (benchmarking) with full transparency to providers and tumor board attendees by disclosing individual ordering provider performance compared to others. These presentations were performed on October 7, 2016 and January 20, 2017.

3) Certification, Accreditation, and Regulation – For educational presentations, we developed specific questions that would qualify for continuing medical education credits.

4) Innovation and Diffusion (of quality improvement strategies) – After introduction of the project described here, there was uniform agreement by tumor board participants with the concept of creating a program to rapidly comply with the updated guidelines, consistent with our recognition of the importance of a day-to-day local quality culture.

5) Workforce Development – Existing within our health care system was a structure in which department chairs, service line directors, and nonphysician administrative leaders had already undertaken education regarding health care quality improvement science as described by the Institute for Healthcare Improvement.[13]

6) Consumer Incentives and Benefits Designs – Information fact sheets containing information on the guidelines were created for patient education at their initial appointment. In these, patients would be encouraged to discuss lab testing and imaging with their provider, as recommended in the Choosing Wisely campaign.[3-6]

7) Payment – To reward and incentivize providers, a plan was discussed to reward them for high guideline compliance with gift certificates to local restaurants.

8) Health Information Technology – Modifications to our existing electronic medical record synoptic documentation template for new breast cancer patients were completed. This included a prompt that would alert providers not to order preoperative CBC and LFTs for patients with early stage I-IIIA breast cancer. If labs were ordered for these patients, a prompt would require documentation of the necessity.

Performance Transparency and Provider Feedback

After initiation of our interventions and a washout period of 1 month (June 2016), we collected, compared, and presented prospective data over the next 6 months (July 1, 2016 through December 31, 2016) to the tumor board. As with our retrospective collection, we looked at overall and per provider compliance with guideline changes, indications for laboratory testing when ordered, and further testing/findings if there were abnormal test results.

Analysis

Analyses included simple frequencies and comparisons of guideline compliance before and after our implementation strategy. We also looked for associations between provider, patient age and stage with guideline compliance by univariate analyses (Fisher's exact test). A P value < 0.05 was considered significant. Trend analyses of guideline compliance overall and by provider at monthly intervals, univariate analyses of test charges by provider, and multivariate analysis of provider and patient characteristics were not appropriate due to small sample sizes. There were 2 patients for which no charge data were available so these patients were excluded from charge analyses. No a priori benchmark (target goal) was established before the date of the implementation strategy, but there was recognition that 100% compliance with breast cancer guidelines was not an appropriate benchmark.[14]

RESULTS

One hundred seven patients presented with early stage breast cancer; 15 patients presented during the June washout period. Overall, 96% (103/107) were female and 4% (4/107) were male. Mean age was 62.8 ± 13.6 years. Distribution of patient age, sex and stages before and after the date of guideline changes were similar (Table).

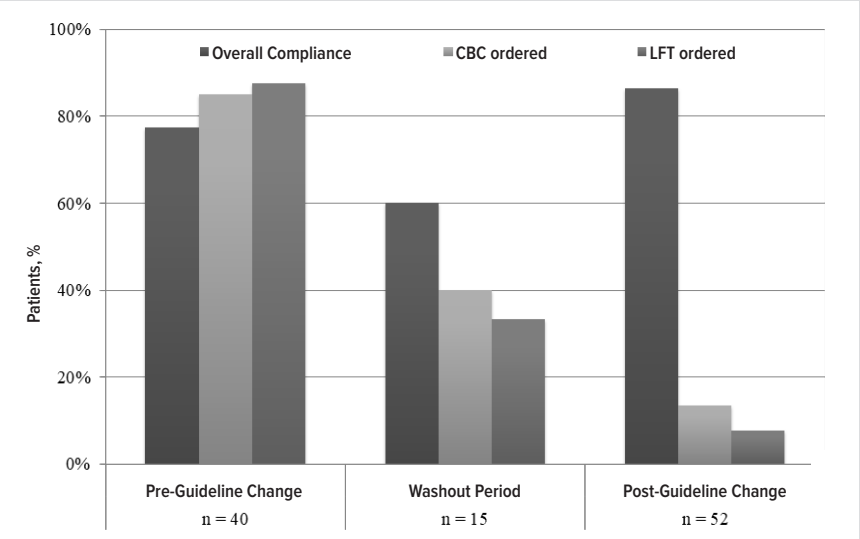
The overall compliance during the entire study time period for ordering a CBC and LFT was 82% (88/107) and 87% (93/107), respectively. Compliance stratified by the pre- and post-guideline change time periods is shown in the Figure. The compliance rate for ordering an individual CBC, stratified by the pre- and post-guideline change time periods, was 85% (34/40) and 87% (45/52) [$P = 0.834$]; for LFT, it was 88% (35/40) and 92% (48/52) [$P = 0.495$]. The mean charge per patient was $97.65 in the pre-guideline period versus $16.96 in the post-guideline period.

Tumor board attendance after the implementation strategy date averaged 14 providers (range 10-19). All tumor boards had at least 1 representative present from each service line that ordered blood tests.

National Quality Strategy Lever Implementation

Levers 1 through 5 described previously were implemented without difficulty. Levers 6 (consumer incentive) and 7 (provider financial incentive) were deemed unnecessary because measured compliance remained high during all audits. Lever 8 (an electronic ordering prompt to recommend against testing) was not available until near the study completion date and therefore did not contribute to guideline compliance.

Figure. Compliance With National Comprehensive Cancer Network Guidelines Over Time



Abbreviations: CBC, complete blood cell count; LFT, liver function test.

DISCUSSION

The evidence for unacceptable variability in the overall quality and cost of health care in the United States is indisputable.[15] In the population of patients with cancer, variability of care also exists as well as evidence of overutilization of tests and treatments. These have been well documented in seminal publications generated by the National Academy of Medicine (formerly the Institute of Medicine), the American Society of Clinical Oncology and others.[3,16-18] Recent examples include delays in the adoption of better diagnostic methods, such as needle biopsy instead of an open surgical biopsy for the diagnosis of breast cancer, and delays in omitting therapies, when safe, such as offering patients omission of postlumpectomy radiation after breast conserving surgery if they receive oral anti-estrogen treatment and are otherwise similar to the patients enrolled in the CALGB 9343 randomized trial.[19,20] Variability of care has even been documented within the participating institutions that constitute the National Comprehensive Cancer Network.[21]

Along with variability, there is increasing recognition of overutilization of care.[3-5,18] For example, Simos et al documented that noncompliant and unnecessary systemic imaging to screen for metastatic disease was performed in nearly 80% of early stage breast cancer patients in Ontario, Canada between 2007 and 2012, and in 2017 identified that over one-third of asymptomatic clinical Stage II breast cancer patients had receipt of chest computed tomography, non compliant with guidelines.[22] As a result of many similar studies, more than 100 professional organizations, including oncology societies, have submitted lists of costly tests and procedures that may not be necessary for optimal patient care.[3-6,22] Such is now the case, for routine ordering of CBC and LFT in patients with early breast cancer.

The National Comprehensive Cancer Network has been a leader in addressing the concerns of overutilization of care by creating evidence- and consensus-based guidelines to improve care and to limit delays in adoption of best practices.[23-25] The efficacy of using its guidelines to improve care has been documented in numerous publications that used compliance with their guidelines as a measure of the quality of care.[25,26]

Despite a robust literature describing delays in the adoption of new evidence- and consensus-based medicine, quick adoption of new changes in guidelines was identified in the in-house audits described here. Guideline compliance has long been part of the established safety and best-practice culture within our institution, as demonstrated by our efforts to monitor compliance with them for more than a decade.[7,8] This is aided by a highly integrated health care system with weekly multidisciplinary clinics and conferences.

Reproducibility

Replicating our findings of rapid adoption of guideline changes could be challenging in less integrated health care systems. For example, we have a physical infrastructure outside of tumor board that promotes ease of interdisciplinary communication as guidelines change. With this structure, all subspecialists and nurse navigators can see the patient concurrently or sequentially (in the same examination room) during breast cancer clinic. Before or after examinations, the entire team can then meet in an adjacent conference room to discuss the patient findings and care guidelines. We also have interoperability of electronic medical records and funding for academic research assistants to audit performance metrics. In the absence of such infrastructure, we would encourage care providers in less integrated systems to utilize real or virtual interdisciplinary tumor boards as a forum to update

providers on guideline changes. Even without interoperability of medical records, electronic synoptic templates can be harmonized between different providers, allowing less burdensome performance tracking.[7] Lastly, implementation strategies that use the National Quality Strategy levers are available to all health care systems.

Study Strengths and Limitations

Our institution has a history of high breast cancer guideline compliance.[7,8] A strength described here is the demonstration that we were able to rapidly achieve guideline deimplementation. By de-escalating the prior routine ordering of preoperative CBC and LFT, we maintained high compliance. As such, we provide support for all providers to adopt continuous quality improvement strategies as a methodology to deliver uninterrupted high quality patient care.[27]

A limitation of our study is that the small sample size and the structure of our breast center limit the generalizability of our findings to other settings.

CONCLUSION

A planned implementation strategy using 7 levers of the National Quality Strategy was successfully executed, resulting in consistently high and sustainable guideline compliance. We believe this format can lead to timely implementation of new evidence-based guidelines at other institutions as well.

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The Clinical Significance of Relative Bradycardia

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ABSTRACT

Introduction: Relative bradycardia is a poorly understood paradoxical phenomenon that refers to a clinical sign whereby the pulse rate is lower than expected for a given body temperature.

Objective: To provide an overview and describe infectious and noninfectious causes of relative bradycardia.

Methods: PubMed and Medline databases were searched using individual and Medical Subject Headings terms including relative bradycardia, fever, pulse-temperature dissociation and pulse-temperature deficit in human studies published from inception to October 2, 2016. The causes and incidence of relative bradycardia were reviewed.

Results: Relative bradycardia is found in a wide variety of infectious and noninfectious diseases. The pathogenesis remains poorly understood with proposed mechanisms including release of inflammatory cytokines, increased vagal tone, direct pathogenic effect on the myocardium, and electrolyte abnormalities. The incidence of this sign varies widely, which may be attributable to multiple factors, including population size, time course for measuring pulse and temperature, and lack of a consistent definition used. The fact that this sign is not consistently identified in case series suggests that relative bradycardia is caused by mechanisms presumably involving or influenced by pathogen and host factors.

Conclusions: Relative bradycardia is a sensitive but nonspecific clinical sign that may be an important bedside tool for narrowing the differential diagnosis of potential infectious and noninfectious etiologies. Recognizing this relationship may assist the clinician by providing bedside clinical clues into potential etiologies of disease, particularly in the setting of infectious diseases and in circumstances when other stigma of disease is absent.

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INTRODUCTION

Under feverish conditions, for each Celsius degree increase in body temperature above 38.3° C (101° F) a corresponding rise in heart rate by 8 to 10 beats/minute is anticipated (Table 1). This finding was first described in the late 1800s by Carl von Liebermeister and is commonly referred to as Liebermeister's rule.[1] The inverse or paradoxical relationship between body temperatures above 38.3° C (101° F) with a pulse lower than expected for the degree of temperature elevation is referred to by the terms relative bradycardia, pulse-temperature dissociation (deficit) or Faget's sign. It has been suggested that relative bradycardia be only applied to cases where body temperature is >38.9° C (102° F), as it is difficult to detect meaningful differences between pulse and temperature at temperatures ≤38.9° C (102° F)[2] as the sign is most sensitive for temperatures > 38.9° C (102° F).[2] This clinical sign may be diagnostically important, particularly when used concomitantly with a detailed patient history, physical examination, and laboratory findings.

The pulse-temperature deficits that occur with relative bradycardia are observed in a limited number of both noninfectious and infectious (Table 2) diseases and conditions. In this review, we provide a comprehensive overview of this underrecognized clinical finding, including relevance to different disease states, diagnostic challenges, and exploration of the pathogenesis of relative bradycardia.

METHODS

PubMed and Medline databases were searched using individual and the following Medical Subject Headings terms: relative bradycardia, fever, pulse-temperature dissociation, and pulse-

Table 1. Expected Relationship Between Pulse and Temperature [1,23]

Temperature	Heart Rate With an Increase of 8 Beats/Minute	Heart Rate With an Increase of 10 Beats/Minute
38.3° C (101° F)	108	110
38.9° C (102° F)	116	120
39.4° C (103° F)	124	130
40.0° C (104° F)	132	140
40.6° C (105° F)	138	150
41.4° C (106° F)	146	160

Table 2. Infectious Causes of Relative Bradycardia (References available upon request)

Type of Infection	Microorganism Family	Infectious Agent	Disease
Bacterial	Chlamydiaceae	*Chlamydia pneumonia*	Chlamydial pneumonia
	Chlamydiaceae	*Chlamydia psittaci*	Psittacosis
	Coxiellaceae	*Coxiella burnetti*	Q fever
	Ehrlichiaceae	*Anaplasma phagocytophilum*	Human granulocytic anaplasmosis
	Ehrlichiaceae	*Ehrlichia chaffeensis*	Human monocytic ehrlichiosis
	Enterobacteriaceae	*Salmonella typhi, Salmonella paratyphi*	Typhoid fever
	Francisellaceae	*Francisella tularensis*	Tularemia
	Legionellaceae	*Legionella pneumophilia*	Legionnaire's disease
	Leptospiraceae	*Leptospira interrogans*	Leptospirosis
	Listeriaceae	*Listeria monocytogenes*	Listeriosis
	Mycobacteriaceae	*Mycobacterium tuberculosis*	Tuberculosis
	Rickettsiaceae	*Orientia tsutsugamushi*	Scrub typhus
	Rickettsiaceae	*Rickettsia rickettsia*	Rocky Mountain spotted fever
	Rickettsiaceae	*Rickettsia typhi*	Murine typhus
	Spirochaetaceae	*Borrelia burgdorferi*	Lyme disease
Parasitic	Babesiidae	*Babesia microti*	Babesiosis
	Plasmodiidae	*Plasmodium vivax, Plasmodium falciparum, Plasmodium*	Malaria
	Trypanosomatidae	*Trypanosoma cruzi*	Chagas disease
Viral	Arenaviridae	*Arenavirus*	Lassa fever
	Bunyaviridae	*Hantavirus*	Hemorrhagic fever with nephropathy
	Bunyaviridae	*Nairovirus*	Crimean-Congo hemorrhagic fever
	Bunyaviridae	*Phlebovirus*	Rift Valley fever
	Bunyaviridae	*Phlebovirus*	Sand fly fever
	Filoviridae	*Filovirus*	Marburg virus, Ebola hemorrhagic fever
	Flaviridae	*Flavivirus*	Yellow fever
	Flaviridae	*Flavivirus*	Dengue fever
	Flaviridae	*Flavivirus*	West Nile virus
	Picornaviridae	*Echovirus*	Acute meningitis
	Pneumoviridae	*Adult human metapneumonovirus*	Pneumonia

temperature deficit. The search was limited to human clinical studies in the English literature published prior to October 2, 2016. We also reviewed bibliographies of retrieved studies as well as reviews for additional relevant studies. Three reviewers independently screened titles, abstracts, and full text of potentially eligible articles to identify studies meeting inclusion criteria. Differences in inclusion were resolved through consensus adjudication. Information was obtained primarily from cohort studies, case series, or case reports. We identified 174 articles that met these criteria. Articles in this review were restricted to those that used the term relative bradycardia in the context of a temperature and pulse relationship, regardless of whether a case definition was applied or how the findings were diagnosed. An additional 21 studies were excluded that used the term relative bradycardia to describe the relationship between pulse and systolic blood pressure.

DISCUSSION

Terminology

Of all the articles identified in this review, the term relative bradycardia was confined to describe the inverse relationship between temperature and pulse rate. Thus, manuscripts that used the term relative bradycardia to describe the inverse relationship between systolic blood pressure and pulse rate in conditions such as trauma,[3-7] acute bleeding,[8-10] anaphylaxis,[11-13] autonomic response,[14-20] and hypovolemic shock [21] were excluded. We believe that the use of the term relative bradycardia in the context of systolic blood pressure-pulse dissociation is a misnomer and, therefore, should be limited strictly to those conditions that describe the inverse relationship between pulse and temperature[2,4,22,23] as originally described. Additionally, relative bradycardia should be applied only to patients in sinus rhythm. Hence, other conditions that slow atrial automaticity and atrioventricular conduction (eg, heart block medications such as antiarrhythmics [eg, amiodarone, digoxin], beta blockers and nondihydropyridine calcium channel blockers [eg, verapamil, diltiazem]), or that have a pacemaker-induced rhythm,[22,24-27] should be excluded from the case definition.

Table 3. Case Series of Relative Bradycardia

Condition	Definition	Total Cases	Cases Evaluated for Sign	% Cases Evaluated	Relative Bradycardia Frequency	% Relative Bradycardia Prevalence	Reference
Babesiosis	Heart rate less than corresponding degree of temperature elevation	17	9	53%	8	89%	47
Dengue	Not defined	50	50	100%	38	76%	56
Dengue	Not defined	24	13	54%	3	23%	57
Hantavirus-induced nephropathy	Heart rate of <90 bpm and fever	471	186	39%	149	80%	58
Legionnaire's disease	Heart rate ≤100 bpm with temperature ≥39.4° C	65	48	73%	28	60%	59
Legionnaire's disease	An increase in heart rate of less than 10 bpm/1° C increase in temperature, with the pulse rate ranging from 38.9° C to 41.1° C	13	13	100%	0	0	60
Legionnaire's disease	Not defined	17	17	100%	9	52.9%	61
Leptospirosis	Heart rate less than 10.2 times the temperature (°C) minus 333.	5	5	100%	5	100%	36
Malaria	Not defined	111	111	100%	15	13.6%	62
Murine typhus	Increase in heart rate <10 bpm for every 1° C increase in temperature	193	193	100%	94	49%	37
Q fever	Heart rate <110 bpm with temperature ≥38.9° C	109	60	55%	44	73%	40,41
Sandfly fever	Not defined	48	22	46%	5	23%	42
Scrub typhus	Increase in heart rate <10 bpm for every 1° C increase in temperature	100	100	100%	53	53%	46
Scrub typhus	Increase in heart rate <10 bpm for every 1° C increase in temperature	237	237	100%	92	38%	37,38
Tularemia	Heart rate <90 bpm over a base rate of 72 bpm for each 1° F temperature elevation	88	62	70%	26	42%	63
Typhoid	Not defined	30	30	100%	8	27%	64
Typhoid	Not defined	7	7	100%	1	14%	39
Typhoid	Not defined	130	101	78%	64	63%	65
Typhoid	A pulse rate less than 100 bpm even during a high fever	130	130	100%	62	48%	66

Abbreviation: bpm, beats per minute.

Conditions that cause degenerative, inflammatory, or infiltrative disease of the myocardium, slowing the ventricular rate, also may mimic relative bradycardia and should be excluded. Therefore, these conditions must be accounted for prior to diagnosis of relative bradycardia.

Causes of Relative Bradycardia

Noninfectious causes — Noninfectious causes of relative bradycardia include lymphoma,[2,22,28] drug-induced fever,[29-32] factitious fever, adrenal insufficiency, and cyclic neutropenia.[28] Drug fever is an obscure cause of fever and often is not considered in the initial differential diagnosis. It coincides temporarily with administration of a drug and disappears after discontinuation of the involved agent.[29-31] It is estimated that drug fever occurs in approximately 10% of hospitalized patients, particularly in the context of antimicrobial medications.[30] In one study, relative bradycardia was identified in 11 of 148 episodes in patients with drug-induced fever.[30]

In addition to relative bradycardia, other clinical clues that may suggest drug fever include lack of fever awareness and the absence of constitutional symptoms.[29-31] Similarly, factitious fever should be considered when patients present with fever and multiple hospitalizations in the absence of other constitutional symptoms. Finally, a case of cyclic neutropenia with periodic fever and relative bradycardia has been reported.[28] It has been proposed that granulocyte colony-stimulating factor (GCSF), IL 6 and tumor necrosis factor (TNF-α) may be involved in not only regulating hematopoiesis but also account for the finding of relative bradycardia in cyclic neutropenia.[28]

Infectious causes — Small sample size, lack of the use of a standard case definition, and reporting of signs limits the ability to draw conclusions regarding the incidence of relative bradycardia in certain infectious diseases. Relative bradycardia has been found to be a nonspecific yet sensitive sign of infection, particularly those caused by intracellular, nonenteric gram-negative organisms[33,34] and may be found early or late in the course of infection, or during the early convalescent period as described with leptospirosis[35,36] and typhoid fever.[37-39] It also may be a marker for delayed fever defervescence, despite appropriate treatment in patients with acute Q fever, scrub typhus, and murine typhus.[37,40,41]

In cases of typhoid fever caused by a gram-negative bacterium, relative bradycardia is identified infrequently in adults (15%-20%) and is absent in children.[34] In addition to infections caused by intracellular gram-negative pathogens, relative bradycardia also is seen in certain viral infections (eg, dengue and sandfly fever),[37,38,41,42] rickettsia bacterial (eg, anaplasmosis and ehrlichia),[43-45] parasitic protozoan (eg, malaria, babesiosis, and Chagas disease),[41,46-50] and leptospirosis (eg, spirochete bacteria) but not brucellosis infections.[2,35,36] It is hypothesized that Lyme disease may also present with relative bradycardia.[51-53]

In addition to dengue and sandfly fever, other viral hemorrhagic fevers (eg, Lassa fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, Ebola hemorrhagic fever, Marburg virus disease, and yellow fever) also are associated with relative bradycardia.[27] Interestingly, dengue, yellow fever, and West Nile virus are all caused by the same RNA virus genus; of note, both Zika virus and tick-borne encephalitis virus are also members of this genus, however relative bradycardia has not been documented—to our knowledge—in these illnesses.[42,43]

Distinguishing Diagnostic Features of Relative Bradycardia Due to Infectious Disease

Differentiating the infectious cause of relative bradycardia can be, in some cases, a diagnostic challenge. These diseases share common presentations of nonspecific fever prodrome, along with constitutional symptoms such as malaise, fatigue, anorexia, chills, myalgia, and headaches. In some cases such as Legionnaire's disease and human granulocytic anaplasmosis, gastrointestinal symptoms including nausea, vomiting, and diarrhea may be present. In contrast, adults with typhoid fever commonly present with constipation.

Evaluation should begin with a thorough history including recent travel history to locations where pathogens are present, exposures to animals, consumption of contaminated water or food, and flea or tick bites. The presence of a rash and its location may provide additional information as to the disease etiology (eg, rose spots are found in 20% to 30% of adults with typhoid fever[28,54] and are confined to the chest, abdomen, and back, whereas the rash of Rocky Mountain spotted fever typically begins on the extremities and spreads to the trunk). The presence of pneumonia with relative bradycardia further narrows the differential diagnosis to Q fever, Legionnaire's disease, psittacosis, scrub typhus, or tularemia.[55] The absence of relative bradycardia in mycoplasma pneumonia and presence in Legionnaire's disease may be an important clinical clue for differentiating these two causes of community-acquired pneumonias. The presence of hepatitis, gastrointestinal symptoms, and pneumonia with relative bradycardia suggests Legionnaire's disease. Exposure to birds (psittacosis), ticks (Rocky mountain spotted fever, tularemia), placental products, or dried dust (Q fever) provide additional information to narrow the differential diagnosis. Thus, the use of this clinical sign if present, along with an accurate occupational, environmental, and avocational exposure history, provides additional clues for obtaining appropriate diagnostic confirmatory tests.

In the majority of case series shown in Table 3, relative bradycardia was typically observed in less than half of patients. However, it is important to note that for several infectious causes of relative bradycardia, not all cases were consistently evaluated for the presence of this sign. In studies where 100% of patients were evaluated, there was a broad range (0%-100%) reported for the incidence of relative bradycardia (Table 3). An important consideration with regard to these findings is that comorbidities, medications (eg, beta blockers, clonidine, and nondihyropyridine calcium channel blockers), and electrolyte abnormalities that may affect heart rate often were not reported. Indeed, hyponatremia, hyperkalemia, and hypokalemia are known to cause bradycardia, and hyponatremia is commonly identified in patients with relative bradycardia and Legionnaire's disease, scrub typhus, or Rocky Mountain spotted fever. Thus, relative bradycardia as a clinical sign may not have predictive value for obtaining a definite diagnosis, but may serve as a feature of specific diseases after other factors that cause bradycardia are accounted.

Pathogenesis of Relative Bradycardia

The incidence of this sign varies widely, which may be attributable to multiple factors including population size, the time course for measuring pulse and temperature, and lack of a consistent definition used. The fact that this sign is not consistently identified in case series suggests that relative bradycardia is caused by mechanisms presumably involving the pathogen and host factors, includ-

ing genetic determinants in response to infection.

The pathogenesis of relative bradycardia remains poorly understood and a variety of mechanisms have been proposed to explain this finding including release of inflammatory cytokines, increased vagal tone, direct pathogen effect on the myocardium, and electrolyte abnormalities. The systemic inflammatory response to infections is complex and involves the interaction of exotoxins and endotoxins from the pathogen and release of pro-inflammatory cytokines (IL 10, IL 6, IL 5, IL 2, IL1α, IL 17, IL 4), tumor necrosis factor alpha (TNFα), and granulocyte macrophage colony-stimulating factors from the host.[32] Some of these pro-inflammatory cytokines such as TNFα, IL 1 and IL 6 increase vagal tone decreasing heart rate. Conversely, vagal stimulation has been shown to decrease the levels of pro-inflammatory cytokines, thus modulating host response to infection.[33] Accentuated vagal response has been a proposed mechanism seen in some patients. Thus, inflammation, with its many mediators (eg, cytokines), can elicit in some patients a cascade of clinical signs and symptoms, including bradycardia, to eliminate potential threats to the host. These factors also are associated with activation of major systems (eg, cardiac, immunological, hematological, and neurological) responsible for systemic responses including bradycardia.

Our review had several limitations, including possibility of reporting biases. We may have missed published studies that were not in the English literature. Studies that we found may have selectively reported outcomes. Most of the studies had risks of bias due to unclear definitions and methods. The lack of a consistent standard for case definition also limited our ability to identify the actual incidence of this sign in various diseases.

CONCLUSION

Relative bradycardia is an underrecognized and underappreciated physical finding. Its recognition can be an important bedside tool for diagnosing infectious and noninfectious etiologies. Relative bradycardia may be a useful marker for diagnosis when other signs and symptoms are confusing or less clear to reveal disease etiology. More research is needed to determine the frequency of this finding in various infections and noninfectious diseases as well as its clinical significance in diagnosis and outcomes. Future reporting also should provide details about methods, apply consistent case definition of relative bradycardia, and specify a priori how outcomes will be measured.

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A Curriculum for Residents to Develop Successful Quality Improvement Projects

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ABSTRACT

Background: Quality improvement (QI) education in residency training has become critical for numerous reasons, but little has been written about factors that lead to successful improvement projects within residency training.

Methods: A quality improvement curriculum for third-year psychiatry residents was developed. The percentage of resident projects that have been successfully implemented was calculated. Residents completed the QI Knowledge Application Tool adapted for psychiatry before and after the curriculum to assess knowledge and skills.

Results: Eighteen of 19 resident projects were successfully implemented. QI Knowledge Application Tool scores improved from 4.8 to 8.1 ($P = 0.0053$) after completion of the curriculum.

Conclusions: Residents are able to implement successful projects and to increase their knowledge and skills in quality improvement when given appropriate resources and incentives.

BACKGROUND

Quality improvement (QI) education in residency training has become critical for several reasons. For example, the Accreditation Council for Graduate Medical Education (ACGME) requires education in QI as a standard for accreditation of residency programs.[1] Residents may also benefit from QI training since maintenance of certification (MOC) requirements after residency now require completion of performance improvement modules.[2] Finally, residents may benefit from preparation for postresidency work in a health care environment that increasingly demands quality outcomes and is based on performance measures.

Few research reports describe residency training programs that result in resident QI projects that are truly successful and sustainably implemented. Most described residency QI curricula are time-limited (often in the form of a 4-week rotation), which may explain the low success rate of resident QI projects.[3] Lack of faculty expertise in QI is also a barrier to educating residents in it.[4] Curricula that combine didactic and experiential learning appear most effective.[5,6] Our objective was to develop a QI curriculum for psychiatry residents at the University of Wisconsin Hospital and Clinics that results in successful QI projects and increased resident QI knowledge and skills.

METHODS

Faculty Development

Faculty development in QI in the University of Wisconsin Department of Psychiatry was undertaken to ensure that faculty members were equipped to teach and mentor residents in QI. During the semester prior to the introduction of the QI curriculum, the Department declared 1 month "UW Psychiatry QI Month," featuring weekly Grand Rounds speakers on a variety of QI topics. This month culminated in a daylong weekend faculty education retreat, which included practical, hands-on workshops addressing QI educational topics as well as an informational talk given by the Wisconsin Medical Society chief medical officer on relevant QI issues within the state of Wisconsin. While UW Psychiatry QI Month was a 1-time event, new core faculty continue to receive training in QI, and current faculty receive ongoing training, via "QI Fact of the Week" emails authored by the QI course director, in which she highlights developments within the QI field, or showcases some aspect of the resident curriculum or projects on which residents are currently working.

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Box. Example of a Resident Quality Improvement Project

Project: Screening patients in a mental health setting for sleep-disordered breathing.

Aim Statement: By June 2015, 80% of University of Wisc. psychiatry residents will screen >60% of their outpatients for sleep disordered breathing on intake.

Rationale: Obstructive sleep apnea (OSA) is common, especially in psychiatric patients. OSA causes psychiatric symptoms. Screening is relatively easy.

Intervention: A screening tool (STOP BANG) was mailed to new patients with their intake packet (academic license obtained for its use). An electronic medical record (EMR) Smart Phrase was made available for use by all residents to document screening. Education of residents on relevance to psychiatry, the screening process, and referral information was undertaken. Residents were provided with an information card with a reminder of the Smart Phrase and sleep referral process.

Outcome: Increased screening by 31% within first 2 months of intervention, and significantly more referrals for sleep studies placed.

Sustainability: This process is now an ongoing part of orientation for residents new to this outpatient clinic. The EMR Smart Phrase is now available to all providers and is embedded into note templates.

Curriculum Development

QI curricula were developed that primarily involved educational experiences for the post-graduate year (PGY)-3 psychiatry residents. This experience included 15.5 hours of didactic seminars, which addressed QI topics including development of an aim statement, plan-do-check-act (PDCA) cycles, involvement of stakeholders in QI projects, principles of survey design for QI projects, patient safety, root cause analysis, MOC and performance in practice modules, and QI Journal Club. It also included 9 months of protected time (10% time per week) for QI project development. During their QI project time, which occurred concomitant with the didactic portion of the curriculum, residents worked in pairs to develop a QI project. They met with an assigned QI faculty supervisor 30 minutes per week, with whom they used an internally developed QI workbook (available upon request) to guide their project. Residents were asked to align their projects with existing quality initiatives, eg, those of our clinic or hospital system, the Choosing Wisely campaign,[7] or others. Content for this curriculum (the entirety of which is also available upon request) was developed based on knowledge gleaned from a number of local and statewide QI-related professional development events attended by the QI curriculum director.

Residents were required to present progress on their projects at numerous time points. This included a midpoint presentation to their classmates and the QI curriculum director, a presentation in the latter third of the year to residents from all classes and the residency training directors, and a presentation to the department's QI Committee at one of its monthly meetings. They presented final results of their projects at department grand rounds at the end of the academic year. In the latter venue, they also displayed a poster in A3 format (a standard format for illustrating QI projects) depicting the results of their projects. In addition to these presentations, the curriculum also included each resident participating in a hospital peer review meeting for psychiatry, and presenting a Morbidity and Mortality case (not one in which they were involved personally) to our department.

Curriculum Tie-In to Maintenance of Certification

As part of this curriculum, residents complete 1 American Board of Psychiatry and Neurology (ABPN) Improvement in Medical Practice module and present the results to their peers. Additionally, residents are informed that if they complete all of the QI curriculum requirements for the year, they may claim ABPN credit for completion of a Patient Safety Course. Such a course is a new requirement as of 2016 for ABPN diplomates that must be completed by the end of the first MOC block. ABPN has granted approval for completion of this requirement as part of residency training, even prior to residents actually becoming board certified.[8]

Data Analysis Methods

The University of Wisconsin Health Sciences Institutional Review Board granted exemption from full review for this study. Spanning the entire 8 years that this curriculum has existed, the percentage of resident projects completed that have been sustainably implemented was calculated. This was based on determination by the curriculum director as to how many projects were continuously incorporated into clinical practice 3 months after completion of the residents' protected time to work on them. The first 2 cohorts of residents participating in the curriculum (N = 16) completed the QI Knowledge Application Tool (QIKAT), adapted for psychiatry (available upon request), before and after the curriculum to assess the effectiveness of the curriculum in increasing resident QI knowledge and skills.[4]

RESULTS

Eighteen of 19 (95%) resident QI projects that have been developed since the start of this curriculum have been sustainably implemented. Example resident QI projects have included improving rates of screening patients in a mental health setting for sleep-disordered breathing (Box), improving resident satisfaction with information provided via paging from nursing staff and improving nursing satisfaction with resident timeliness in response to pages, improving the psychiatry consultation-liaison sign-out process, and increasing smoking cessation clinic referrals from an inpatient unit. Some resident QI projects have been published[9] or have received national attention and grant dollars[10] for their continuation after completion of the residents' rotation.

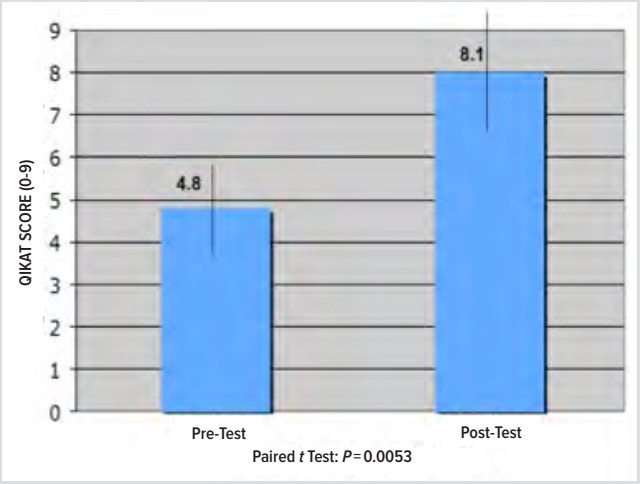
QIKAT scores improved from an average of 4.8 to 8.1 (maximum score 9) as measured by paired *t* test ($P = 0.0053$) (Figure).

DISCUSSION

This study demonstrates that psychiatry residents are able to implement successful QI projects, and to increase their knowledge and skills in QI, when given appropriate resources and incentives. It is important to try to determine which factors are important in the success of a program's residents in implementing QI projects, since many programs have reported difficulty with successful implementation of resident projects.[3] This conclusion was reached both through literature review of those factors associated with success (or lack thereof) in implementing and sustaining projects, as well as through incremental evolution of this curriculum over the 8 years it has been in existence, correlating with improved project quality.

Longitudinal duration of time dedicated to the quality improvement curriculum is likely the most important factor in the success of this program's residents in implementing QI projects. It takes time to research best practices or benchmarks; appropriately involve all relevant stakeholders; gather baseline, interim, and final data; and run multiple PDCA cycles. A 1-month rotation, reportedly common for QI rotations within residency programs,[3] will likely not allow careful completion of all of those steps. Resident protected time for QI project development also appears to be an important factor, so that projects are not completed in haste in small amounts of time once other clinical work is completed. Protected daytime hours often are needed for meetings with stakeholders and discussions with information technology staff who can provide clinical data. Provision of protected time conveys to the residents that QI work is important and worthy of significant attention. Additionally, we have found that automatically scheduled weekly meetings with faculty QI project supervisors, who help with selection of measurable projects that can realistically be completed during the course of the rotation, are critical. We initially did not schedule these meetings for residents and rather informed them that their supervisors were available for help with projects when needed. That approach did not lead to regular meetings between supervisors and residents. Residents also are kept accountable via several interim project presentations, such that they do not have the option of waiting until the end of the rotation to put together a project. Full participation in the QI curriculum is incentivized via offering of ABPN MOC credit in advance of residency graduation only for those residents who complete all required aspects of the curriculum. Project work is also incentivized via provision of opportunities for publication and presentation of the projects in numerous venues. For example, in requiring residents to print A3 posters depicting the results of their projects, we inform them that these posters would likely be acceptable for presentation at several local, regional, and even national QI or research symposia. Anecdotally, they have appreciated these opportunities, which require little additional work beyond the time they are already putting into the requirements for the QI curriculum. Finally, we developed rotation evaluations (available upon request) that reward success and sustainability of projects.

Figure. Effectiveness of Quality Improvement (QI) Curriculum in Increasing Resident Knowledge and Skills in QI as Measured by Precurriculum vs Postcurriculum QI Knowledge Application Tool (QIKAT) Scores, N=16



Strengths of this study include the 8-year longitudinal evolution of this QI curriculum leading to incremental improvements through application of QI methodologies to the curriculum itself, in turn resulting in improved project quality and sustainability. Limitations of this study include that it represents a single specialty at a single institution. However, quality improvement is a universal process that transcends specialty, and very few aspects of this curriculum would not be applicable to all specialties. The program described in this report is also fortunate to have many resources dedicated to its quality improvement curriculum, and that may not be feasible for all programs.

Future directions may include study of this type of curriculum within a broader audience of residents or fellows, impact of this curriculum on future incorporation of QI principles into post-residency work, and ultimate impact of this curriculum on quality of patient care.

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A Case of Optic Neuritis Secondary to Lyme Disease

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ABSTRACT

Introduction: Optic neuritis is a condition associated with various systemic diseases, such as multiple sclerosis, and is also considered a rare complication of Lyme disease.

Case: A 46-year-old white woman presented with sudden onset of bilateral vision loss. After extensive workup, she was diagnosed with Lyme optic neuritis based on the clinical presentation and positive serology. She was treated with doxycycline for 2 weeks.

Discussion: Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi*. The most commonly affected areas include the skin, joints, heart, and nervous system. Lyme optic neuritis is a challenging diagnosis and therefore often underreported. Doxycycline or ceftriaxone for 2 weeks are recommended for treatment.

Conclusion: We report this case to increase awareness among clinicians to include Lyme disease in the differential diagnosis of optic neuritis for unexplained cases of vision loss, particularly in Lyme endemic areas.

INTRODUCTION

Lyme disease (Lyme borreliosis) is a multisystem zoonotic disease caused by the spirochete *Borrelia burgdorferi.*[1] In the United States, the primary mechanism of transmission of Lyme is through the bite of its vector, the *Ixodes scapularis* tick.[2] Incidence of Lyme disease in the United States is greatest in the Northeast, Mid-Atlantic, and North Central regions.

The clinical presentation of the infection has been well described in the literature.[2] Most patients (60%-90%) present with erythema migrans, more commonly known as the "bull's-eye" rash, initially in the location of the bite. Flu-like symptoms (fever, headache, myalgias) may be present in the first few days after the bite.[3] Individuals may progress to have cardiac (carditis and atrioventricular block) and neurological (meningitis, cranial nerve palsies) symptoms in the early disseminated stage and musculoskeletal (oligoarthritis) symptoms in the later stage without treatment.[1]

Optic neuritis, described as the inflammation of the optic nerve resulting in blurred vision and eye pain, is a rare complication of Lyme disease. Despite a few published cases of Lyme optic neuritis, a causal link between the infection and ophthalmological manifestation has not been well-established.[4,5] Here we report a case of a patient with recent Lyme infection complicated by bilateral optic neuritis.

CASE REPORT

A 46-year-old white woman from northern Wisconsin with a past medical history of hypertension, asthma, Lyme disease (diagnosed and treated with a course of doxycycline 10 years ago), posttraumatic stress disorder, depression, seizure disorder (last seizure at age 21), and alcohol use disorder presented to the emergency department (ED) with progressive blurring of her vision and paresthesias for 3 weeks duration. The patient reported that her blurry vision began after she had upper respiratory tract symptoms. She also reported having nausea, weakness, dizziness, and tingling/numbness of her bilateral lower extremities. Of note, the patient endorsed visual hallucinations.

Thirteen days prior to her presentation, the patient had gone to an outside optometrist who had documented optic head edema and instructed her to go to the ED for evaluation. She did not go to the ED at that time. Her worsening vision finally prompted her to go to the ED. Upon her arrival, she was found to be hypertensive with a blood pressure of 154/124 mmHg. She was afebrile. Physical examination including neurological exam was unremarkable.

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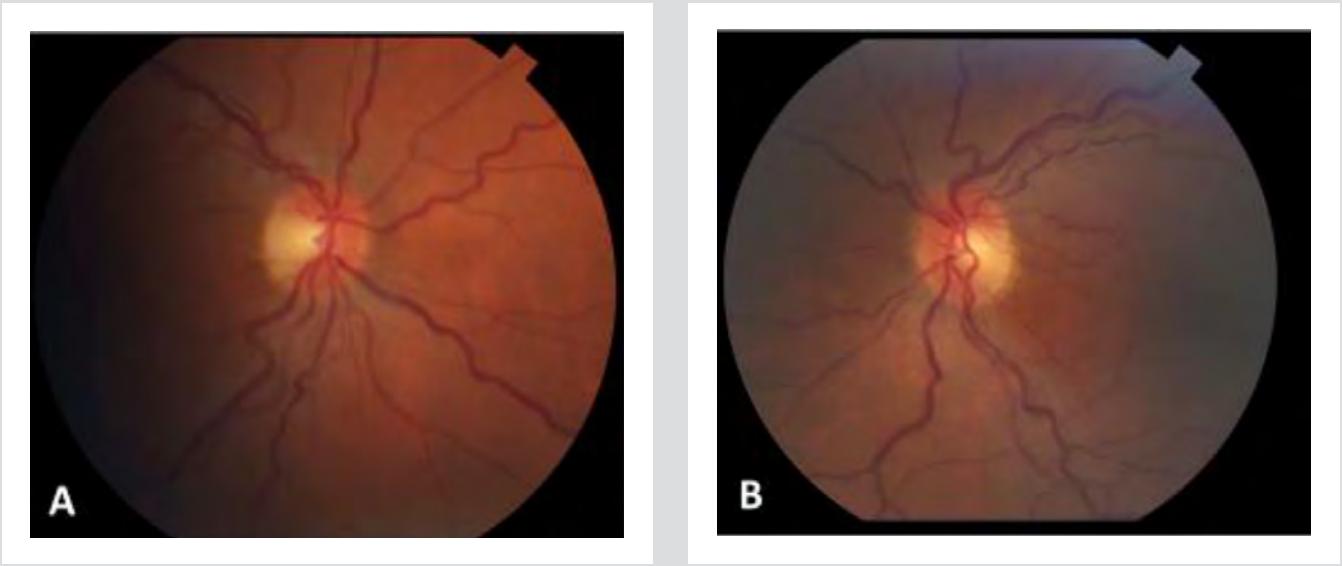
Figure 1. Color Fundus Photos of Patient's Right and Left Eye



A. Right eye shows obscuration of the nasal border of the optic disc consistent with grade 1 optic nerve head edema. B. Left eye reveals mild blurring of the entire optic disc border along with elevation of the nasal aspect of the optic nerve. Both eyes exhibited retinal vessel tortuosity.

Visual acuity with Snellen Eye Test Charts was 20/400 in both eyes and color vision using the Hardy-Rand-Rittler color plates was 2/6 in the right eye and 0/6 in the left eye. The pupils were equal, round, and reactive bilaterally without afferent pupillary defect, and extraocular movements were full without pain in any direction. A dilated fundus exam demonstrated bilateral optic head edema, hyperemia, and optic nerve elevation concerning for intracranial hypertension (Figure 1).

Admission laboratory results were within normal limits except for elevated transaminases with aspartate aminotransferase (AST) 329 unit/L (Normal: 11 – 33 unit/L) and alanine aminotransferase (ALT) 146 unit/L (Normal: 6 – 37 unit/L), which were thought to be related to her chronic alcohol use.

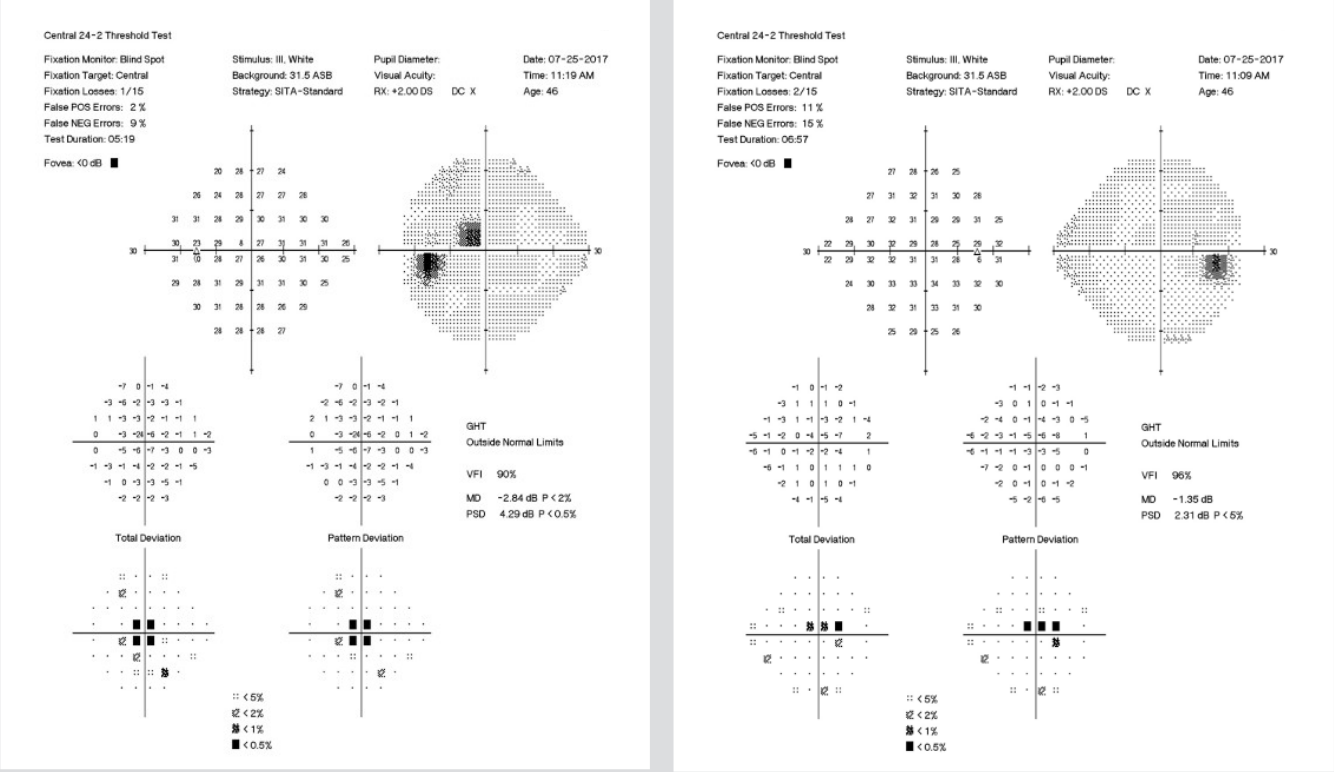
Based on the recommendations from neurology and ophthalmology, she had an extensive workup to rule out other causes for vision loss and paresthesia. Computed tomographic scan of head without contrast was negative, and magnetic resonance imaging of brain with orbits was unremarkable except for nonspecific white matter lesions. An automated perimetry visual field test showed cecocentral visual field defects in both eyes (Figure 2). A lumbar puncture showed normal opening pressure, and glucose, protein, and cell count were within normal limits. There was no cerebrospinal fluid (CSF) pleocytosis. Final CSF cultures, Lyme and West Nile Viral serologies were pending at time of discharge. She had normal results for other tests including Venereal Disease Research Laboratory (VDRL) test; rapid plasma reagin (RPR); C-reactive protein; sedimentation rate; antinuclear antibodies; C3 complement; C4 complement; total complement; CCP antibody; rheumatoid factor; Quantiferon-TB; HIV 1,2 AB; Hepatitis C antibody; Hepatitis B surface antigen; Hepatitis B surface antibody; cardiolipin antibodies; beta-2 glycoprotein 1 antibodies IgA/IgM; urine heavy metal screen; and lupus anticoagulant panel.

The inpatient workup ruled out posterior reversible encephalopathy syndrome, idiopathic intracranial hypertension, multiple sclerosis, meningitis (viral, fungal, tuberculosis, syphilis, and other bacterial), autoimmune process and cerebrovascular disease. She was discharged home in stable condition with outpatient neuro-ophthalmology follow-up.

A week later, the serum immunoassay for Lyme disease resulted in elevated IgG/IgM antibodies of 1.39 (reference 0.00-0.90 in situ hybridization), and the Western blot was positive for serum IgM Lyme antibodies but negative for IgG antibodies. More specifically, 2 bands (P41 IgM, P23[Osp C] IgM) were positive in addition to the positive Western blot, which fulfilled the Centers for Disease Control and Prevention (CDC) recommendation for a positive Lyme test.[6] The CSF Lyme study only was positive for 3 IgG antibody bands (P39, P41, P45) with a negative Western blot. Based on the clinical presentation and the positive serologies, the patient was diagnosed with optic neuritis and peripheral neuropathy secondary to Lyme disease.

On further questioning, she did not recall any recent tick bite. She was evaluated by neuro-ophthalmology and infectious disease as outpatient and was started on doxycycline 100 mg twice daily for 2 weeks. The patient was again admitted a week later with alcohol intoxication. Upon questioning, she endorsed some improvement in vision after initiation of antibiotic. However, the patient left against medical advice and was not adherent with her follow-up appointments. Whether her symptoms resolved completely thereafter is unknown.

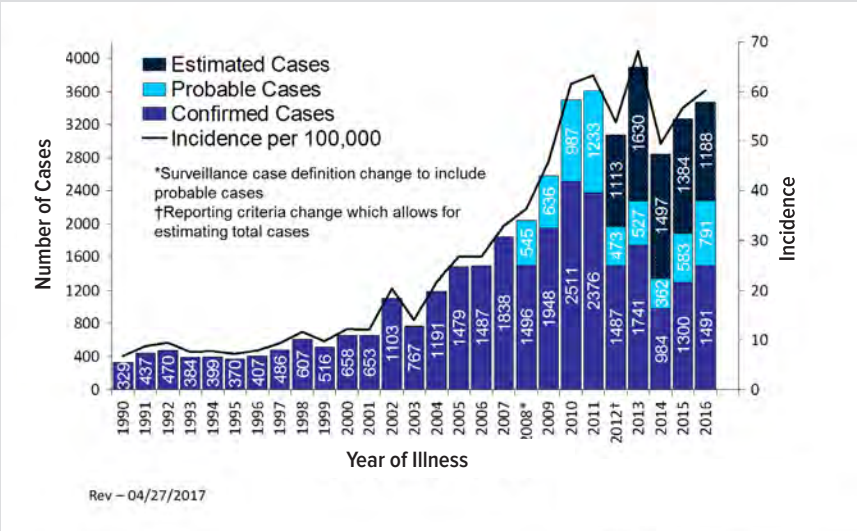
Figure 2. Humphrey Visual Fields of Patient's Right and Left Eye



Humphrey Visual Fields shows cecocentral defects in both eyes, with greater prominence in the left eye.

At the time of her diagnosis, we had asked the patient to elaborate on her past exposure to Lyme disease. About 10 years prior she had presented to her primary care doctor complaining of fever, rash, and arthralgia. At the time, she was treated successfully with doxycycline based on the clinical presentation and positive Lyme serology. Since she had acquired this care elsewhere, documentation of this encounter was not available in our system. Therefore, limited details were provided by the patient and her daughter, both of whom were poor historians.

Figure 3. Reported Cases of Lyme Disease in Wisconsin, 1990-2016 (n = 41,864)



Source: Wisconsin Department of Health Services website: www.dhs.wisconsin.gov/tickborne/lyme/index.htm. Accessed June, 2018.

DISCUSSION

Lyme disease was first recognized in the United States in 1975 at Lyme, Connecticut. It mostly occurs in the Northeast, Mid-Atlantic, and the North Central regions of the United States.[2] According to Wisconsin Division of Public Health Bureau of Communicable Diseases, the highest number of cases in Wisconsin is seen in the western and northern regions and cases have increased in the central region and eastern region in the recent years. With more than 38,000 cases reported between 1980 and 2015, it is the highest reported tick-borne disease in the state. In 2016, about 1,491 confirmed cases of Lyme disease (*Borrelia burgdorferi*) were reported to Wisconsin Department of Public Health (Figure 3).

The most commonly affected areas include the skin, joints, heart,

Box. Sibony's Criteria for Strong Evidence of Optic Neuritis Associated With Active Lyme Disease Diagnosis [5]

Strong evidence requires the following core elements:

1. Optic neuritis.*
2. Endemic exposure.*
3. Negative Venereal Disease Research Laboratory test or Rapid Plasma Reagin.*
4. Exclusion of multiple sclerosis.*
5. Positive Lyme titer (enzyme-linked immunosorbent assay [ELISA] or Indirect Fluorescent Antibody).*

One of the following must be associated as well:

- Encephalitis/Meningitis with CSF pleocytosis, intrathecal antibody production, or CSF polymerase chain reaction positive *B. burgdorferi* DNA and positive Western blot.
- Recent Lyme disease signs (such as facial nerve palsy, arthritis or radiculoneuritis) with positive serum ELISA confirmed by Western blot.
- Recent diagnosis of erythema migrans by a physician, usually with flu-like symptoms.

* Elements the reported case fulfilled.
Abbreviation: CSF, cerebrospinal fluid.

and nervous system. Fever, headache, malaise, arthralgia, myalgia, and erythema migrans may be the initial presentation. Weeks to months after the initial infection, patients with untreated Lyme disease may develop early disseminated disease that can include migratory musculoskeletal pain, carditis, facial nerve palsy, ocular manifestations, meningitis, or radiculopathies. Approximately 10% to 15% of patients with untreated Lyme disease will develop neurologic manifestations.[7]

Optic neuritis is a common manifestation of central nervous system disease in various autoimmune, inflammatory, and infectious processes.[8] While Lyme disease has been known to involve both the central and peripheral nervous systems, its association with optic neuritis is poorly understood.[9] Lyme optic neuritis is a challenging diagnosis and, therefore, it is underrecognized and underreported. Few cases of Lyme optic neuritis have been published in the literature. While rare, Lyme optic neuritis should be considered in the differential diagnosis when managing patients with visual symptoms in Lyme-endemic regions. Other possible etiologies of optic neuritis should be ruled out before this diagnosis is made.

Our patient fulfilled the criteria for acute Lyme infection following the 2-tiered serology test (positive immunoassay followed by a positive Western blot) recommended by the CDC.[6] Our case also fulfilled the criteria for acute Lyme disease with strong evidence of a causal link with optic neuritis, as described by Sibony (Box).[5] It is unclear why our patient's CSF only showed the presence of 3 IgG bands (P45, P41, P39) of 5 required for a positive CSF Western blot. Additionally, no IgM bands were present in the CSF despite the patient's neurological symptoms. Intrathecal antibody production is not observed in all patients with Lyme disease, and is common in some ethic groups more than others (more in Europeans than Americans).[9] A negative test for Lyme antibody in CSF cannot exclude central nervous system (CNS) disease. Nevertheless, pleocytosis, which was not seen in our patient, is a finding that is more likely to be seen with CNS involvement.[9,10] Despite the unique laboratory results, our patient's neurological symptoms improved after treatment was initiated, which continues to support the association of her Lyme disease with optic neuritis. Unfortunately, due to the patient's nonadherence to follow-up, we were not able to acquire more details on her recovery. Nevertheless, there continues to be lack of data and guidelines surrounding Lyme-related optic neuritis, a field in which future study is warranted.

Our case is unique due to not only the patient's prior exposure to Lyme disease, but also the lack of traditional Lyme presentation (tickbite, fever, rash, arthralgia) during the most recent infection. The onset and symptomatology were not consistent with those of post treatment Lyme disease syndrome (PTLDS), which manifests as persistent symptoms even after antibiotic treatment rather than a reestablishment of symptoms as seen with our patient.[11] Additionally, optic neuritis is not included in the clinical spectrum of PTLDS. It is not likely that our patient's neurological changes are due to a relapse of her initial infection, as there is no scientific evidence revealing the persistence of *Borrelia* after treatment with antibiotics.[12] Rather, taking into account her exposure risk, it is more likely that she acquired a second Lyme infection. However, there is a paucity of literature on the use of serological testing for the diagnosis of reinfection,[13] and it is uncertain whether her previous history of Lyme disease affected her current serologies and complicated establishing a strong association between Lyme disease and her optic neuritis.

In summary, the diagnosis of Lyme optic neuritis involves a history with possible tick exposure, optic nerve edema or elevation, and a workup to rule out other systemic illness and positive Lyme serologies in blood or CSF.

Ceftriaxone, cefotaxime, penicillin G, and doxycycline are indicated in the treatment of most neurological Lyme cases.[8] Oral doxycycline achieves spirochetocidal concentration in the CNS and is highly effective in Lyme meningitis, cranial neuritis, and radiculoneuritis. Two weeks of antibiotic treatment is recommended for neuroborreliosis. The cases available in the literature have been treated with both parenteral and oral antibiotics, and no consensus exists on definite recommendations for the treatment.

Lyme optic neuritis is a diagnosis of exclusion. Therefore, early recognition and treatment is crucial to prevent permanent vision loss.

CONCLUSION

Lyme disease is an uncommon cause for optic neuritis, but it should be considered in the differential diagnosis of unexplained vision loss and optic nerve edema, particularly in Lyme-endemic

areas. Detailed examination and investigation are important to make the diagnosis of Lyme optic neuritis. We report this case to increase awareness among clinicians to include Lyme disease in differential diagnosis of optic neuritis. More reporting of the cases is essential to draw enough attention from the clinicians and researchers to help devise evidence-based guidelines on the approach to diagnose and manage this condition.

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Distal Tibia and Foot Involvement in a Patient With Waldenstrom's Macroglobulinemia

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ABSTRACT

Bone lesions are a rare presentation in Waldenstrom's macroglobulinemia patients. Although lytic bone lesions and generalized osteoporosis have been described variably in literature on Waldenstrom's macroglobulinemia patients, distal long bone and foot involvement has not been described to our knowledge. We report a patient with Waldenstrom's macroglobulinemia with IgM monoclonal spike, plasmacytic infiltration of bone marrow, and symptoms of foot pain, and found to have distal tibia and foot involvement. The symptoms of bone lesions in our patient were significantly improved with radiation treatment. The possibility of distal involvement of long bones in a clinically relevant presentation should be kept in mind in these patients.

INTRODUCTION

Waldenstrom's macroglobulinemia is a B cell neoplasm characterized by the plasmacytic lymphocyte infiltration and proliferation of bone marrow or lymphatic tissue and IgM monoclonal gammopathy.[1] Traditionally, it has been believed that Waldenstrom's macroglobulinemia is not associated with much osseous involvement. However, several case reports suggest the presence of lytic bone lesions and other bone lesion morphologies associated with Waldenstrom's macroglobulinemia, but the distal involvement of the long bones is not well described in the literature.

We report a patient with a longstanding diagnosis of Waldenstrom's macroglobulinemia who had received multiple therapies over the years, and then presented with biopsy-proven bilateral distal long bone involvement in the form of tibia and foot bones. This report and review of the literature is aimed at a better understanding of clinical and radiographic skeletal assessment in Waldenstrom's macroglobulinemia patients with relevant clinical presentation.

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CASE REPORT

An 80-year-old woman presented with complaints of pain along with swelling in her right ankle, toes, and dorsum of foot. She denied any history of preceding trauma. There was no associated fever, warmth, or redness of the foot or ankle. The swelling was not relieved by limb elevation or trial of furosemide. She had been diagnosed with Waldenstrom's macroglobulinemia 23 years prior. On bone marrow exam at presentation and subsequent exams, plasmacytoid lymphocytes and plasma cells were both increased at 19.1% (normal, <5%) and 7.6%. (normal, <5%) On flow cytometry of bone marrow aspirate, 25% lymphocytes were seen with the majority being B-cells having lambda light chain restriction (CD5 and CD10 negative). She had received multiple chemotherapeutic regimens at different times including chlorambucil, fludarabine, 2-chlorodeoxyadenosine, rituximab, dexamethasone, and bortezomib in varying combinations with variable responses since her diagnosis.

Upon examination, she had evidence of pes planus, limitation of the range of motion of the ankle, and absence of pain throughout the arc of motion. Ankle radiographs showed diffuse nonspecific swelling of the foot with osteopenic bones without any acute fractures (Figure 1). Bone scan was suggestive of significant hyperemia near the right ankle and the proximal foot and also along the lateral aspect of the left foot, consistent with an active inflammatory process (Figure 2). Magnetic resonance imaging (MRI) of the right lower extremity revealed multifocal lesions at the tibia, fibula, talus, calcaneus, medial navicular, 1st metatarsal base, and medial cuneiform. The most pronounced foci were seen at the distal tibia, talus, calcaneus, and medial navicular. There were regions of presumed small soft tissue extension and most likely represented extensive lymphomatous involvement of these osseous structures (Figure 3).

Subsequently, she underwent computed tomography-guided biopsy of prominent medial tibial lesion. Histopathology in conjunction with the flow cytometry was suggestive of low grade B cell lymphoma consistent with lymphoplasmacytic lymphoma with-

Figure 1. Ankle, Radiograph of Foot

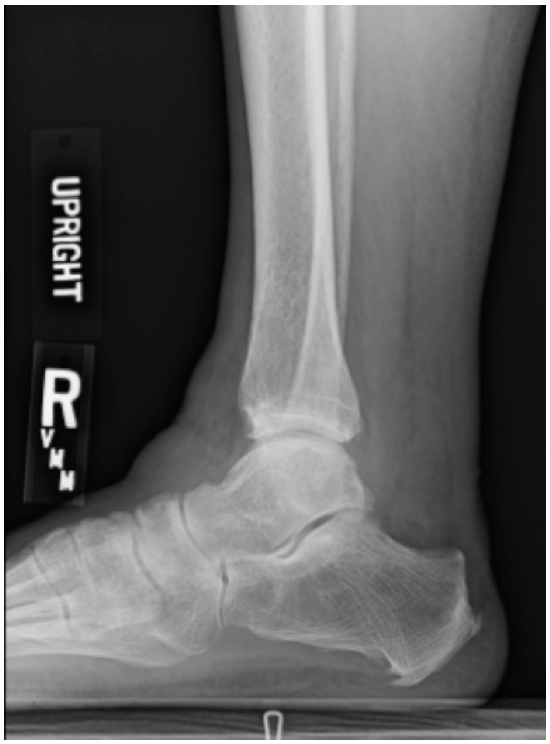
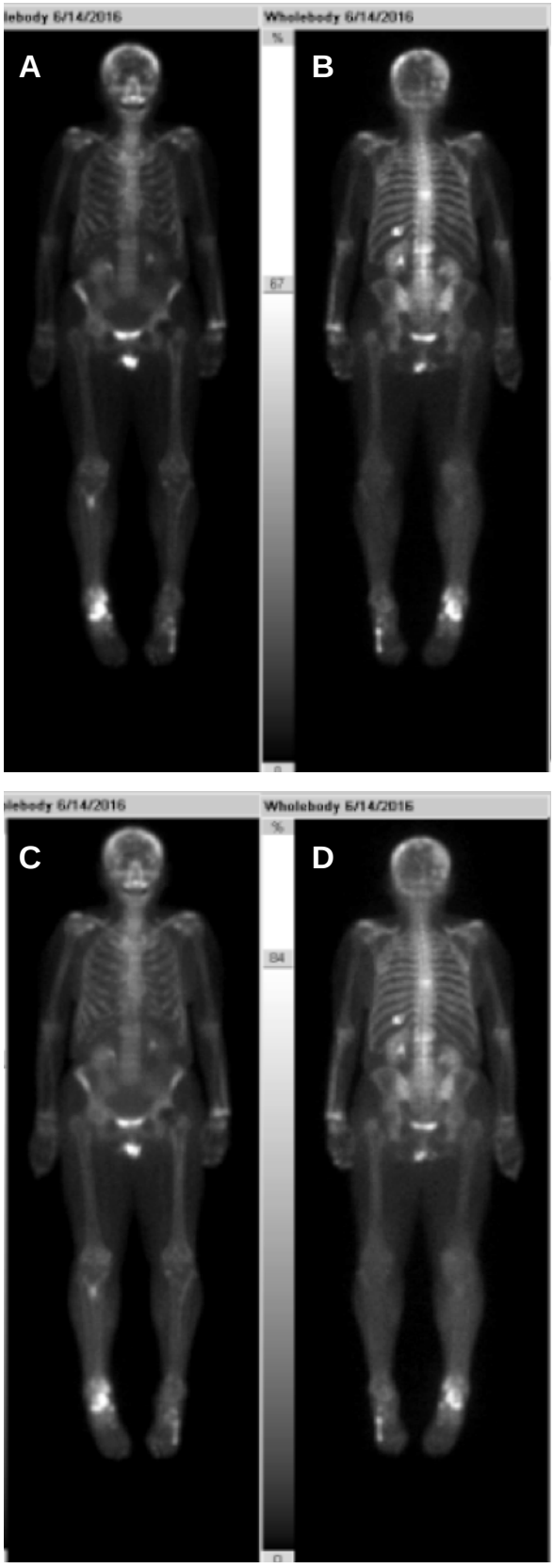


Figure 2 Increased Uptake in Right Distal Tibia and Foot Region on Bone Scan



out any evidence of large cell transformation. Immunoperoxidase staining of the tissue was CD20 positive (Focal) consistent with previous rituximab treatment, CD3 positive (normal T Cells), Kappa/Lambda chronogenic in situ hydridization non-contributory. After receiving local treatment to the right ankle and foot with radiation therapy, the patient achieved significant relief of her symptoms.

About 2 months later, she developed similar pain in her left foot and ankle. MRI revealed multiple osseous lesions within the left foot and ankle that were compatible with areas of lymphomatous involvement. Specifically, the 5th metatarsal shaft was the most pronounced, as the marrow was essentially replaced with presumed tumor. The patient then underwent radiation treatment for these lesions, which relieved her symptoms significantly.

DISCUSSION

Waldenstrom's macroglobulinemia is a B cell disorder characterized primarily by the bone marrow infiltration of lymphoplasmacytic cells and the presence of IgM monoclonal gammopathy. According to the Revised European-American Classification of Lymphoid Neoplasms and World Health Organization classifications, this condition is considered to be lymphoplasmacytic lymphoma.[1,2] As per international workshop criteria, Waldenstrom's macroglobulinemia is defined by IgM monoclonal gammopathy

Figure 3. Distal Tibia and Foot Bone Involvement, MRI Images

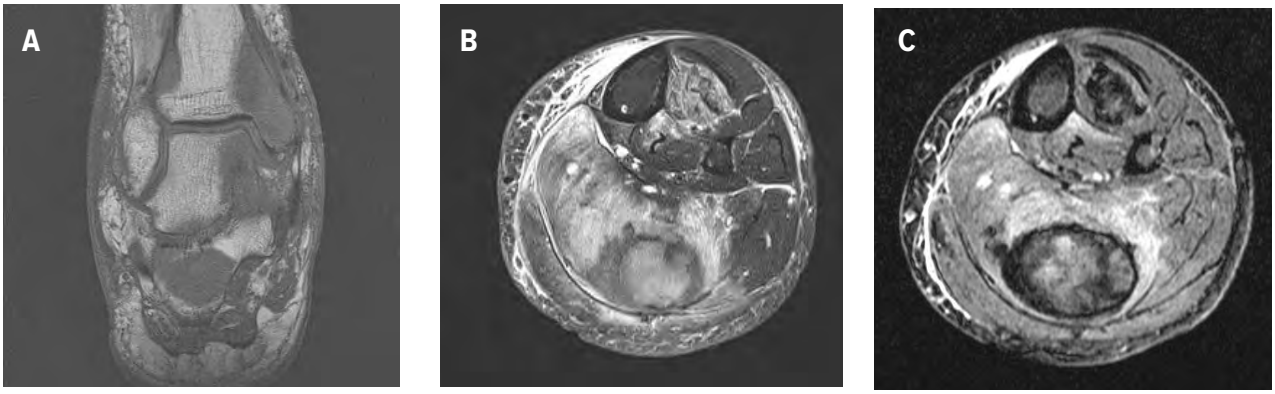


Table. Current Literature on Bony Involvement in Waldenstrom's Macroglobulinemia

Authors	Article Tye	No. of Cases	Lesion Distribution
Leb et al,[5] 1977	Case series	24	Osteolytic lesions with pathological fracture of proximal shaft of right humerus. Osteolytic lesions in skull, clavicles, scapulae, humeri, ribs, and femurs.
Vermess et al,[6] 1972	Case series	41	Lytic bone lesions in skull, vertebral bodies, pelvis, femur, humerus, clavicles, scapula, ribs. Extensive demineralization of bones with vertebral compression in 3 cases.
Ju et al,[7] 2001	Case report	1	Pathological compression fracture in T6-T7 with presence of posterior epidural mass.
Schlesinger et al,[8] 2000	Case report	1	Osteopenia along with pathological fractures of metacarpal bones and right tibia. Multiple lytic lesions found in appendicular skeleton.

of any concentration, bone marrow infiltration by small lymphocytes plasmacytic/plasma cells along with the diffuse, and interstitial or nodular pattern of bone marrow infiltration with $CD19^+$ and $CD20^+$, and surface IgM positivity with variable CD5, CD10, and CD23 positivity.[3]

None of the reports described in the literature have documented the distal involvement of long bones and feet by the Waldestrom's macroglobulinemia tumor like our patient had. The involvement in our case was biopsy proven and confirmed with immunophenotyping. The scarcity of reports on such presentation of Waldenstrom's macroglobulinemia prompted us to report this patient and review the available scientific literature on this topic (Table).

When Waldenstrom's macroglobulinemia was initially described by Waldenstrom in 1944, bony involvement was originally considered to be a differentiating criterion between Waldenstrom's macroglobulinemia and multiple myeloma.[4] Subsequently, Leb et al reported a series of 24 cases confirmed with immune electrophoresis and documented osteolytic lesions. These involved pathological fractures in the proximal shaft of the right humerus and osteolytic lesions in areas such as the skull, clavicles, scapulae, humeri, ribs, and femurs. In this series, the distribution of the bone lesions was mainly proximal.[5] Osteolytic lesions also were prevalent in a case series of 41 patients reported by Verness et al.[6] Of these patients, 19.5% had extensive lytic bone lesions in the skull, vertebral bodies, pelvis, femur, humerus, clavicles, scapula, and ribs. Extensive generalized demineralization in 7 patients, of which 3 had vertebral compression, also was noted. Only 4 patients in their series had lytic lesions involving proximal long bones (mainly femur and humerus) that were radiographically indistinguishable from the multiple myeloma lesions. Symmetric, cyst-like lesions in suprapubic portions of iliac bones also were seen in 3 patients. Notably, distal long bone involvement was not reported in this series.

Our patient also had back pain with subacute pathologic compression fracture of T8 on MRI but no sign of bony lytic lesions in the vertebrae. Ju et al reported a case of Waldenstrom's macroglobulinemia with pathological compression fracture in T6-T7 along with presence of posterior epidural mass in the same region.[7]

Our patient had evidence of osteopenia in the affected bones; Schlesinger et al similarly noted marked osteopenia in their patient. They also saw pathological fractures of the metacarpal bones and right tibia, along with multiple lytic lesions in the appendicular skeleton without any distal bony involvement.[8]

Limitations of the cases in the reported literature may be due to the difficulty in differentiating IgM myeloma from Waldenstrom's macroglobulinemia, especially with the cases diagnosed prior to immune phenotyping and cytogenetics. Recent advances in cyto-

genetics include presence of t (11, 14) in IgM myeloma and total absence in Waldenstrom's macroglobulinemia.[9] Similarly, 6q deletion was reported to be associated with Waldenstrom's macroglobulinemia in another study by Schop et al.[10] Cytogenetic analysis revealed our patient had 6q deletion as well. Other significant molecular markers for Waldenstrom's macroglobulinemia are the myeloid differentiation primary response 88 (MYD88), L265P mutation (seen in ~90% of cases) and CXCR4 (seen in ~30% of cases) since they are both almost exclusively present in MYD88-mutated Waldenstrom's macroglobulinemia.[11] Markers like these can be helpful in distinguishing between Waldenstrom's macroglobulinemia and multiple myeloma.

CONCLUSION

The diagnosis of Waldenstrom's macroglobulinemia should not deflect a clinician from the fact that the bone lesions may be present. Therefore, a bone survey and further investigations may be needed based on clinical presentation, even if symptoms involve distal long bones. The detection of such lesions is significant in view of their implications for symptomatic treatment and also by providing new insights into Waldenstorm's macroglobulinemia diverse clinical manifestations.

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Sanjay Asthana, MD

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The Aging Imperative—Innovations in Research, Education, and Care in Geriatric Medicine

Sanjay Asthana, MD; Robert N. Golden, MD

Over the past century, the number of older adults in the United States and throughout the world has increased dramatically. In Wisconsin today, individuals aged 65 and over comprise more than 15% of the population, accounting for more than $7.9 billion of Medicare spending annually. Since 1900, in the United States alone, the number of persons aged 65 years and older has increased more than three-fold, and this segment of the population is projected to exceed 98 million by 2060, comprising nearly 25% of the population at that time. This remarkable demographic shift has major societal and economic implications, including health care utilization and expenditures, economic growth, and intergenerational and intragenerational equity.

The University of Wisconsin (UW) School of Medicine and Public Health's (SMPH) Division of Geriatrics and Gerontology, one of the premier such divisions in the country, supports state-of-the-art clinical, research, and educational programs in geriatrics and healthy aging. With substantial support from the National Institutes of Health (NIH), Department of Veterans Affairs (VA), and SMPH, the division sponsors several internationally renowned programs in aging research.

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Aging Research Programs at the SMPH

This portfolio targets common age-associated diseases and applies the full spectrum of research, including basic science, translational, clinical, community-based, and dissemination studies. External reviewers often comment on the innovation, translatability, and direct relevance to patient care that characterize the research activities. The focus of the school's current aging research programs includes Alzheimer's disease (AD), biology of aging, care transitions, dysphagia, health disparities, and dissemination and implementation.

The Division of Geriatrics and Gerontology—within the school's Department of Medicine—is home to the NIH -funded Wisconsin Alzheimer's Disease Research Center (ADRC), the nation's only geriatrics-based ADRC led by a geriatrician. The ADRC's overarching scientific goals are to discover novel preclinical biomarkers of AD and their utility for early diagnosis, and to foster a better understanding of the mechanisms underlying the disease's pathology and progression.

The ADRC is internationally renowned for its research in neuroimaging and cerebrospinal fluid biomarkers of AD in at-risk populations. Under the auspices of the ADRC and the Wisconsin Alzheimer's Institute (WAI), the SMPH's AD research program features Investigating Memory in Preclinical AD-Causes and Treatment (IMPACT) and the Wisconsin Registry for Alzheimer's Prevention (WRAP), two large, NIH-funded studies of adult children whose parents have AD. Together, these studies involve the largest and longest-followed cohort of more than 2,000 middle-aged adults at risk for AD. Over the years, collaborative studies involving IMPACT and WRAP participants have identified novel brain imaging and cerebrospinal fluid biomarkers that could identify persons who have AD pathology without any symptoms. Such individuals will be ideal candidates for clinical trials of emerging treatments and prevention strategies that could slow or stop AD progression at asymptomatic stages.

The Division of Geriatrics and Gerontology also sponsors multiple extramurally funded aging research programs in areas other than AD, such as:

- Molecular studies in the biology of aging

Box. Characteristics of the UW School of Medicine and Public Health Division of Geriatrics and Gerontology

- One of the largest geriatrics divisions in the United States
- Supports a large, interdisciplinary, translational research program in aging with substantial extramural funding, currently exceeding $73 million
- Houses a National Institutes of Health-funded Alzheimer's Disease Research Center
- Provides state-of-the-art primary and specialty care to older, frail patients from across Wisconsin and beyond
- Supports a large training program in geriatrics for learners of varied levels and backgrounds

around the theme of **metabolism of aging**.

- **Care transitions research** evaluating the utility and validity of Coordinated Transitional Care, an innovative, nurse-led, low-cost model of care targeting older, frail adults transitioning between multiple clinical settings;
- Studies examining the **efficacy of lingual and oropharyngeal muscle strengthening** in reducing dysphagia in patients with stroke and dementia.
- **Health disparity and equity research** focused on African American and Native American populations.
- Community-based studies assessing the efficacy of **multidisciplinary interventional programs** through a community-academic aging research network that involves a unique partnership between UW-Madison faculty members and community-based workers.

Interdisciplinary, Patient-Centered Geriatric Clinical Programs

UW Health sponsors multiple ambulatory and inpatient clinical care programs that provide evidence-based approaches for delivering exceptional care to older, often frail adults with multiple comorbidities. The inpatient program includes a multidisciplinary consultation team comprised of a geriatrician, pharmacist, social worker, advanced practice provider, dietician, and physical or occupational therapist who evaluate complex patients admitted to various medical and surgical wards at University Hospital. The majority of consultations focus on classic geriatric syndromes—including delirium, cognitive deficits, and mobility impairments—and result in interventions that enhance coordination of care, reduce the incidence of polypharmacy, decrease rehospitalization rates, and improve quality of care. Ambulatory programs include multiple primary care and specialty clinics in the areas of memory impairment, falls, sleep disorders, geriatric oncology, and comprehensive geriatric evaluation. Overall, specialty care constitutes about 60% of geriatric practice at UW Health and adheres to the principle of patient comanagement with referring primary care physicians throughout Wisconsin and beyond.

Training the Next Generation of Physicians, Researchers, Clinician Educators, and Other Health Care Professionals in Geriatrics

The Division of Geriatrics and Gerontology has nationally acclaimed educational programs that train learners from varied backgrounds, including medical students, residents, fellows, nurses, pharmacists, social workers, and speech-language pathologists.

To date, the Geriatric Medicine Fellowship Program has trained more than 100 physician fellows; of these graduates, over half are pursuing academic careers across the country. Notably, some fellows have become prominent leaders who are directing geriatric programs at major institutions around the nation and world. Educators within the division collaborate with key partners at the Medical College of Wisconsin, Marquette University, and Aurora Healthcare in Milwaukee. Several serve on the US Health Resources and Services Administration-sponsored Wisconsin Geriatrics Workforce Enhancement Program. This initiative focuses on developing innovative educational programs that support primary care providers in delivering competent care to older adults throughout the state. With support from an NIH T32 training grant and VA fellowships in advanced geriatrics and older women's health, the Division of Geriatrics and Gerontology trains up to 12 postdoctoral and physician fellows in aging research each year. Most of the program's graduates now serve on the faculties of academic institutions or in research positions at pharmaceutical companies.

The Division of Geriatrics and Gerontology is advancing the health of our growing older population through innovative research, clinical, and educational programs. Its faculty members make novel discoveries in all aspects of aging research, which are translated into improved care and widely disseminated. The division's clinical programs provide state-of-the-art primary care and specialty consultations for complex older patients, and its educational programs provide competency-driven, outcomes-based training to learners of all backgrounds and training.

Breast Density Notification Law Requires New Patients Notifications

Jennifer Bergin, MD; Alicia Arnold, MD

Wisconsin's new Breast Density Notification Law, 2017 Wisconsin Act 201 (Assembly Bill 653), requires facilities that perform mammograms to notify women categorized as having heterogeneously dense or extremely dense breast tissue (BI-RADS density categories C and D) about their condition.

Signed in April, the law makes Wisconsin the 35th state to pass breast density legislation. Representative Mike Rohrkaste authored the bill at the request of a constituent who was diagnosed with advanced breast cancer after dense tissue masked the tumor on her mammogram.

Facilities that perform mammograms are now required to include language that is substantially similar to the following sample language in, or along with, their required patient results letters:

Your mammogram shows that your breast tissue is dense. Dense breast tissue is found in almost 40 percent of women and is a normal finding. However, studies show that dense breast tissue can make it harder to find cancer on a mammogram and is associated with a slightly increased risk of breast cancer. Regular screening mammograms are still recommended for you. This information is provided to raise your awareness about the result of your mammogram. You can use this information to talk with your health care professional about your own risks for breast cancer. Together, you can decide which screening options are right for you. The results of your mammogram were sent to your doctor. Please note that breast density is affected by several factors and may change over time.

Patients who receive these notices most likely will seek guidance and ask questions, eg, whether any supplemental screening is recommended. There is currently insufficient evidence to support the routine use of additional screening tests beyond mammography in women whose only risk factor is dense breast tissue. However, for patients who have dense breast tissue, it may be useful to conduct a risk assessment to determine if additional screening is recommended. Many health systems' electronic medical records have a built-in assessment tool, or there are several online screening tools, including the following:

- Tyrer-Cuzick model, version 8 (includes breast density): http://ibis.ikonopedia.com
- Bright Pink: https://www.brightpink.org
- Gail risk model: https://www.cancer.gov/bcrisktool/

To further assist clinicians and their patients, the Wisconsin Radiological Society, with support from the Wisconsin Medical Society, has developed a set of FAQs and compiled a number of resources (Boxes 1 and 2). One particularly useful tool for physicians may be clinical scenarios, which address a variety of patient situations and the recommended actions in flow chart format.

While these resources are hopefully useful in assisting clinicians and patients in understanding the new law and notifications, each situation is unique and will require assessment as well as individual patient and physician discussion to determine the correct course of action.

Box 1. Patient Resources

- ACR Breast Density brochure: https://www.acr.org/-/media/ACR/Files/Breast-Imaging-Resources/Breast-Density-bro_ACR_SBI.pdf
- Website: https://www.areyoudense.org
- Mayo consumer site: https://www.mayoclinic.org/tests-procedures/mammogram/in-depth/dense-breast-tissue/art-20123968
- Website: http://densebreast-info.org

Abbreviation: ACR, American College of Radiology.

Box 2. Clinician Resources

- Clinical Scenarios: https://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/pdf/117/2/Breast_density_scenarios-2018.pdf
- Frequently Asked Questions: https://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/pdf/117/2/Breast_density_FAQs.pdf
- ACR position Statement on Breast Density: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Reporting-Breast-Density
- ACR Position Statement on Higher-risk Women: https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Breast-Cancer-Screening-in-Women-at-Higher-Than-Average-Risk
- Supplemental Screening for Breast Cancer in Women with Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5100826/pdf/nihms826317.pdf

Abbreviation: ACR, American College of Radiology.

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- Legal Requirement for Opioid Prescribing in Wisconsin
- How to Decrease Prescription Drug Abuse: The What, Why and How
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- Interacting With the Drug-Seeking Patient

**Programs denoted with (*) have been approved by the MEB to fulfill the 2-hour continuing medical education requirement on responsible opioid prescribing per Med 13.30(3) of the Wisconsin Administrative Code. Other programs in this series may be combined to fulfill that requirement.*

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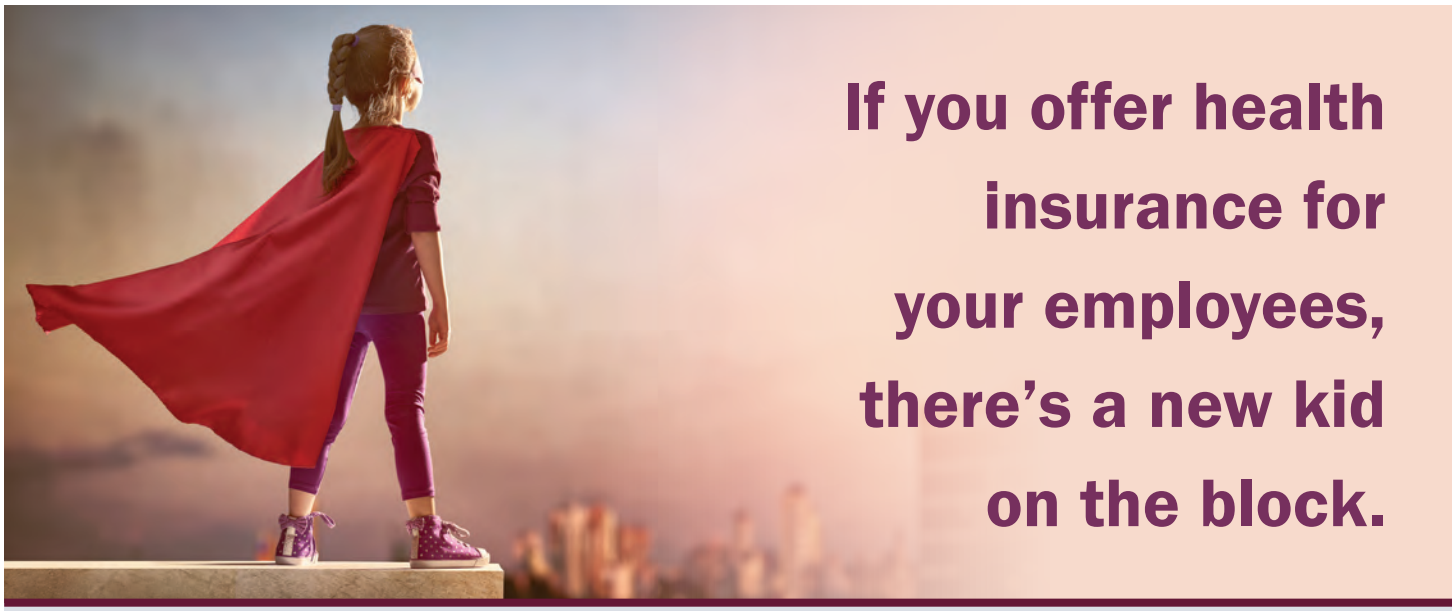

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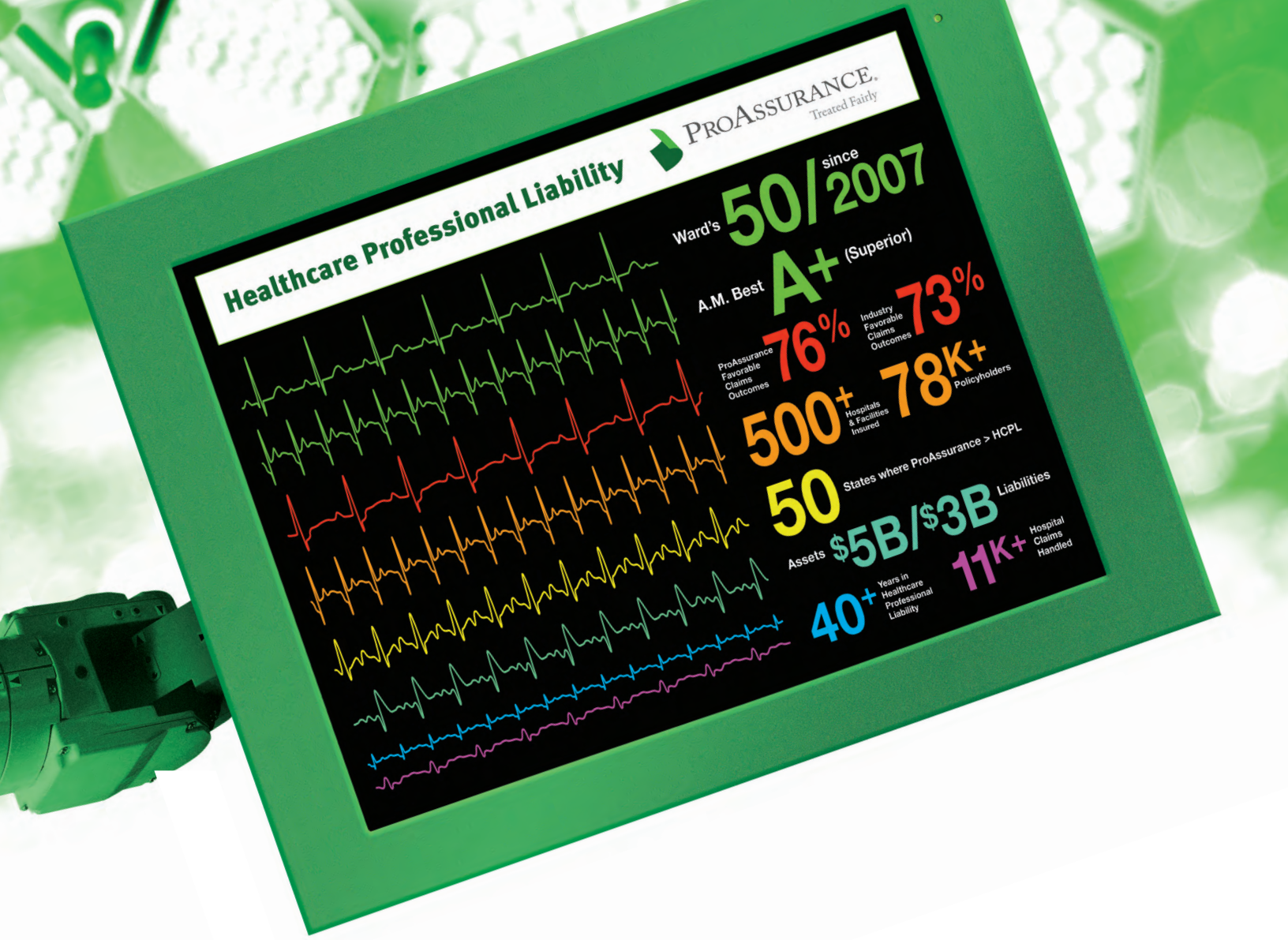

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