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Human Genome Sequencing

What to do with incidental findings when treatment isn't available

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WMJ

COVER THEME

Human Genome Sequencing: What to do with incidental findings when treatment isn't available

In addition to its potential to provide findings of clinical benefit, whole genome sequencing also has the potential to identify incidental findings—some for which no treatment is available. A study in this issue of *WMJ* considers the debate around how and which findings should be returned to patients, as well as their desires for such results.

Cover design by Mary Kay Adams-Edgette.

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Paucity of Laboratory-confirmed Failures of High-dose Influenza Vaccine in an Elderly Population, 2012-2013

Last year we reported our experience with high-dose influenza vaccine, which bolstered the view that high-dose vaccine was more effective than standard vaccine in preventing laboratory-confirmed influenza in the elderly.[1] Accompanying commentary[2] noted that this evidence was welcome, albeit weak. Additionally, the commentary noted the disproportionate impact of influenza on the elderly, the disappointingly low efficacy of influenza vaccine, and the interest in results of clinical trials. Subsequently, the results of a randomized, controlled trial (RCT) of 31,989 patients have been reported, showing 24.2% better efficacy of high-dose vaccine in preventing laboratory-confirmed clinical influenza.[3] These results increase interest in confirmatory observational studies. Observational studies and RCTs produce similar results,[4] and observational studies reflect less-selected populations, unlike the RCT,[3] which required subjects who were available for weekly phone contact for 3 months and twice weekly contact for 2 months. Consequently, we looked at our more recent experience with high-dose vaccine. This strengthened our observations by providing data from an additional year—one which was particularly troublesome for the elderly[5]—and analyzing the data with more rigorous statistical methods.

As in 2010-2011,[1] the high-dose vaccine was used overwhelmingly for those 65 and over in the Veterans Health Administration's Nebraska-Western Iowa Health Care System, but sister facilities in our region's Veterans Integrated Service Network (VISN) 23 overwhelmingly used standard vaccine. VISN 23 laboratories documented 90 positive influenza tests among 67,993 standard vaccines and 8 positive tests among 11,320 receiving high-dose vaccine. (Sample odds ratio 1.87, Fisher exact test 2-tailed, P=.04921). Our institutional review board approved this study.

Although consistent with our previous results and the RCT[3] (odds ratio 1.3257), this data has limitations resembling those of our earlier report: variation in laboratory methods and decisions to test, geographic variation in impact of influenza, absence of research staff to control data quality, and confounding by herd immunity. Our odds ratio exceeded that of the RCT, possibly reflecting an older population; the RCT odds ratio was 1.49 for those 75 and older.[6] The larger amount of vaccine compared to 2010-2011 may reflect trends in vaccine use.

We agree with the observation that our earlier report has limitations, as does efficacy of standard vaccine. For that reason, the current report is important in providing additional support to the RCT[3], showing that high-dose vaccine is an improvement in protecting the especially vulnerable elderly population.

Marvin J. Bittner MD; John M. Horne MD; Medical Service, Omaha Veterans Affairs Medical Center, VA Nebraska-Western Iowa Health Care System, Omaha, Neb

Acknowledgement: We thank Chris Wichman for statistical assistance. This letter does not represent the views of the Department of Veterans Affairs.

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WMJ

A Method of Treating Common Colds

By Harrington and Richardson in the Manual of Practical Hygiene

Editor's note: The following editorial was originally published in WMJ, *Volume 13, p. 494, May 1915.*

Common colds, or inflammation of the respiratory tract, localized either in the upper or lower portion of said tract, are extremely common, and are undoubtedly of a contagious nature.

The exact relationship of the various organisms found in the secretions to the pathological condition is not by any means clear.

Colds of this type are oftentimes more uncomfortable than immediately dangerous, but they may be, undoubtedly, in some instances followed by more severe and even fatal infections.

Persons suffering from such colds should, therefore, be isolated, as far as that may be possible, and every effort should be made to render the secretions of the nose and mouth harmless.

In this connection attention may be called to a method of local disinfection said to have been practiced successfully among employees of a large city department store.

"A small saucepan, or the bottom of a chafing-dish, heated by an alcohol lamp or gas stove, is to set up in a small room, such as a bathroom. Use a pint of water, in which has been put five teaspoonfuls of formalin (Schering's).

"The person with a cold in the head, the nearer the beginning of it the better, goes into the room in which this vaporizing outfit has been started. Doors and windows are closed. The patient does not get close to the apparatus, but sits any place in the room, perhaps reading a book, and stays there as long as it is possible to breathe, till it seems, indeed, as if the next breath would cut like a knife. It usually takes about eight minutes. The patient then turns out the lamp and leaves the room. One such treatment will stop a cold in its first few hours. Two or three treatments at four-hour intervals will suffice on the second day of the cold."

The success attending this method of treatment of common colds would certainly warrant its trial in more serious infections of the respiratory tract.

Information Is Not Knowledge and Certainly Not Wisdom

John J. Frey, III, MD, Medical Editor

Almost from the time the sequencing of DNA was finally described, the genetic imperative to know more about the function of genes, chromosomes, and their connections with health and illness has driven the science of human genetics. Scientists wanted to know how risk works its way into our genetic structure and, more importantly, what is the predictive value of genetic changes. Many genetically linked illnesses and syndromes were described far in advance of their cause being understood. Down syndrome, for example, was described in the mid 1800s, but the cause was not known until 100 years later. Since genetic sequencing became better understood and the technology made it less expensive (the cost of a genome has gone from over $100,000 in 2002 to less than $5000 in 2014 and is rapidly moving toward $1000)[1] there has been a great rush to commercialize genomic sequencing that has outstripped our ability to understand and interpret the clinical significance of all the information.

The article by Strong and colleagues[2] in this issue of *WMJ,* while a local study, raises many questions that are problematic if their findings are more generalized. They surveyed a group of coding staff members about whether the subjects would want both actionable and non-actionable genomic information about themselves or their families. While genetics professionals indicated they would want actionable information but not information of no apparent use, the study subjects, who are more typical of the lay public, by a large majority said they would want all available information—about themselves and their children. The authors raise a number of concerns about their results that are important to read.

Unmediated access to clinical information in the United States has been driven by the country's belief in the technological imperative but also has contributed to the extraordinary use—and overuse—of technology by physicians. Patients read about something that has just been approved and want it tried on them and are often unwilling to wait until it has been tested against other available technology or placebos.[3] Physicians, particularly generalists, spend an undue amount of time correcting assumptions that come from patients about the value of such untested technology and, in the age of consumer-driven medicine, often simply give up and do it. It is hard to follow the admonition "don't ask the question unless you are willing to deal with the answer" when a patient sees a test as a right. The admirable goal of more transparency in research often conflicts with the overly enthusiastic portrayal of that research by media from *The New York Times* to consumer blogs. Whole body scans, cardiac calcium scans, meniscectomy for knee pain,[4] and packaged multichannel analyzers were just a few of the technologies that were widely advertised and used prior to being re-evaluated with well-designed placebo-controlled trials.

Unmediated access to clinical information in the United States has been driven by the country's belief in the technological imperative but also has contributed to the extraordinary use—and overuse—of technology by physicians. Patients read about something that has just been approved and want it tried on them and are often unwilling to wait until it has been tested against other available technology or placebos.

In contrast to handing genetic testing results to a patient, the family history has historically been a part of every patient's chart. All medical students, presumptively, are taught how to "elicit" a family history. The problem

is that ticking boxes on computer lists has become the way doctors gather family histories rather than having a conversation about what runs in families. I was taught to gather information with genograms, which are more dynamic representations of family relationships that include psychological and geographic information, as well as disease-linked data.[5] Box ticking without having discussion of meaning—what does it mean that a relative has had cancer, heart disease, neurological problems, or depression—neglects the purpose of gathering such information.

Most doctors would consider it unethical to just send a letter to a pregnant woman or post results of prenatal screening in her electronic medical record (EMR) without having a personal conversation to assess her understanding of the results or, better, to find out whether she wants the tests in the first place.

However, many of us have personally had experiences with tests posted without explanation. The EMR is not a substitution for communication. In the same way, "personalized medicine," contrary to the way it is portrayed in the media, is not a simply a genome that we mix and match with risks and benefits like a crossword puzzle. Unfortunately—and Strong's study alludes to this—the public may be very far along in its belief that more genetic information, even information for which there is little or no use, is preferable. Physicians will be challenged to show patients that wise use of appropriate information rather than information itself is in the best interest of all involved. But they have to be willing to spend the time to explain, which, in the age of the 15-minute encounter, raises all sorts of other issues.

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Views of Nonmedical, Health System Professionals Regarding the Return of Whole Genome Sequencing Incidental Findings

Kimberly A. Strong, PhD; Kaija L. Zusevics, PhD, MPH; David P. Bick, MD; Regan Veith, MS

ABSTRACT

Background: Use of genome sequencing in the clinic continues to increase. In addition to its potential to provide findings of clinical benefit, it also has the potential to identify findings unrelated to the indication for testing (incidental findings). Incidental findings are the subject of considerable debate, particularly following the publication of recommendations by the American College of Medical Genetics and Genomics. This debate involves how and which results should be returned as well as stakeholders' desires for such results. Part of the difficulty in determining best practice in relation to returning incidental findings is the dearth of empirical data available regarding laypersons' attitudes and desire for the sometimes controversial information.

Methods: In an effort to contribute data on views regarding the return of incidental findings following genome sequencing in a clinical setting, a survey specifically designed around the various types of incidental findings that occur, ranging from clinically actionable to nonactionable, was administered to a nonmedical population of medical coders working at a medical school (N = 97). Almost all (98%) of the respondents were women, 80% had 6 or more years of experience as a medical coder, and about three-fourths (74%) of participants reported that they had children.

Results: The group surveyed was considerably more interested in receiving all types of results for both themselves and their children than previously surveyed genetics professionals.

Conclusion: Results from this study offer a snapshot of opinions beyond those of the professional genetic community and demonstrate a striking difference between genetic professionals and a more lay population in terms of their attitudes and desires regarding the return of incidental findings. Additional research is needed to explain the nuances in the perspectives motivating these variations.

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INTRODUCTION

Sequencing of the exome and of the entire genome (together referred to as clinical sequencing in this report) has entered clinical practice.[1,2] It is able to diagnose rare genetic disorders,[3] suggests treatments for cancer patients,[4] and rapidly identifies inherited disorders in newborns.[5] Use of clinical sequencing in direct-to-consumer (DTC) genetic testing also may expand.[6]

When clinical sequencing is used in medical practice, testing may uncover incidental (or secondary) findings. Incidental findings (IFs) in this context are DNA changes (variants) of varying clinical significance that are unrelated to the indication for testing. Some will be pathogenic variants, while many will be benign variants or variants of uncertain significance.[7] As our understanding of these variants increases, the number of IFs that could alter medical management (actionable findings) will increase. (Actionable findings are defined as gene variants that are associated with an increased risk for a particular disease or condition for which there are "established therapeutic or preventative interventions, or other available actions, that have the potential to change the clinical course of the disease."[8])

In addition, an increase is expected in the number of IFs for conditions for which there are no interventions currently available that may change the disease prognosis (nonactionable findings). Laboratories rely on several important elements when determining whether or not a variant will be reported as actionable or nonactionable, including medical reports, policy statements, lab regulatory bodies, and state and federal statutes. Additional factors or influences include personal utility or degree to which the individual may use the information to take action regarding a

specific portion of their lifestyle, reproductive decision-making, or employment. One such policy statement was issued by the American College of Medical Genetics and Genomics (ACMG), which aimed to provide guidelines for physicians and laboratories involved in genomic sequencing.[9] However, this practice statement was not universally accepted, particularly its recommendation that certain incidental findings should be reported "without reference to patient preference."[9] Criticisms regarding this approach were raised[10-12] and the ACMG subsequently released a revision stating "patients should have an opportunity to opt out of the analysis of medically actionable genes when undergoing whole exome or genome sequencing."[10] At present, there is little empirical data to help physicians and laboratories decide how best to involve patients in this decision making.[13] Yet, it has been suggested that clinicians may face liability if they fail to disclose an IF that could result in an intervention that improves health outcome.[14]

Survey information concerning the return of IFs found through clinical sequencing is starting to emerge. Green et al[15] questioned 16 specialists in clinical genetics and/or molecular medicine. They were asked to select variants in 99 common conditions that they would return to the ordering physician if discovered incidentally through clinical sequencing. In only 21 conditions did all 16 agree in favor of disclosure—for adult-onset conditions with a known pathogenic mutation. Another survey of 279 clinical genetics professionals examined attitudes towards IFs identified through clinical sequencing.[8] The authors found that the vast majority of respondents were interested in learning about actionable IFs in themselves (96%) and in their child (99%). There was far less agreement concerning nonactionable findings. Just 44% wanted to know about IFs related to adult-onset nonactionable disorders in themselves, and 31% wanted to know such information about their child. A recently published study of 258 primary care providers demonstrated very similar results.[16]

Lohn et al[17] distributed an online questionnaire to 496 geneticists and genetic counselors in Canada to ascertain their views concerning disclosure of IFs from clinical sequencing. Responses from the 210 participants varied depending on the nature of the finding; 95% recommended disclosure of an IF pertaining to a serious and treatable condition, while only 12% recommended disclosure of an IF with only social implications (eg, nonpaternity). It is important to note that the majority of genetic counselors (84%) and geneticists (79%) indicated that families should be given a choice as to which kinds of IFs are returned to them.

In addition to the survey data above, a recently published study involved focus groups of 35 genetics health professionals.[18] While participants demonstrated a diverse range of views regarding the return of genomic results, overall, patient autonomy was deemed a vital component in the decision-making process.

Data also exists concerning patient/family preference regarding return of genomic research results[19] as well as the public's preference concerning informatin about ancillary risk associated with particular pharmacogenetic test results.[20] However, with regard to clinical sequencing, there is a paucity of data pertaining to the views of the general population and individuals who are likely to be the beneficiaries of IFs. Townsend et al[21] used 3 focus groups—genetics health care professionals, the general public, and parents whose children have experienced genetic testing—to explore attitudes about the disclosure of IFs in clinical sequencing. A significant divide was identified. Professionals expressed a preference to limit analysis in order to avoid IFs as much as possible and focus pretest discussions primarily on medical relevance. In contrast, the lay groups in this study emphasized autonomy and patients' rights to choose what findings they receive and felt that patients would accept the consequences of any potential anxiety and uncertainty engendered by the results.

Continued guidance on IFs from the medical and ethics community is essential; however, more information is needed from the general population and individuals who are the likely beneficiaries of this technology. To further survey attitudes toward the return of IFs, we engaged nonmedical health system professionals (lay professional members of an academic department in a medical school) around this issue as a step towards evidence-based guidelines that involve all stakeholders.

MATERIALS AND METHODS

Study Sample and Recruitment

Following a 45-minute presentation about basic genetics concepts and clinical genetics care presented by one of the authors (DB), attendees at the Medical College of Wisconsin's (MCW) Billing and Collections Team (BCT) meeting in February 2013 were invited to participate in a voluntary, anonymous survey. This method was similar to a previous administration of the same survey.[16] The purpose of the lecture preceding the survey was to provide a broad overview of genetics and genomics in clinical practice to a general audience. Lecture topics included the definition of basic genetic concepts (gene, chromosome, inheritance), examples of patient populations that would benefit from genetic testing, overview of how genetic diseases are cataloged, inheritance patterns (autosomal recessive, autosomal dominant, x-linked, mitochondrial, chromosomal), penetrance, variability, prenatal genetic topics (age-related risk, fertility, preconception risk assessment, screening, diagnostic testing, chorionic villus sampling, amniocentesis, ultrasound examination, reproductive options, preimplantation genetic diagnosis), genetic screening, ethnic-related disease incidence, disease specific examples that highlight the previous definitions (cystic fibrosis, Tay-Sachs disease, thalassemia, sickle cell anemia, Down syndrome), example

of the clinical diagnostic considerations for a disease category exemplified by neurodevelopmental disorders, examples of how a known genetic diagnosis or risk can be used to benefit patients, definition of whole exome/genome sequencing and when they are clinically indicated, definition of primary and secondary results, and definition and examples of both adult- and childhood-onset medically actionable and nonactionable diseases. The same diseases used as examples in the survey were used in the lecture. The BCT is composed largely of support staff members who fall in the category of "professional health care support occupation." They are responsible for coding the professional component of evaluation and management services and/or procedures rendered by MCW faculty, serving as liaisons for patient complaints, responding to insurance organization inquiries, and/or providing education to faculty. The group's leader stated that overall, these professionals have an intermediate to advanced knowledge of coding conventions and functionalities, anatomy and physiology, and medical terminology, suggesting a potential aptitude for medical topics such as genetics. The BCT meets regularly to offer continuing education credits for staff members who are accredited by the American Academy of Professional Coders (AAPC).

Survey Development and Data Collection

A 23-item questionnaire (by Lemke and colleagues[8]) that was previously developed, vetted, and used by internal and external experts was administered to assess participants' attitudes regarding whole genome sequencing (WGS) for themselves and their children, as well as their views about the return of results in 3 distinct areas: (1) types of WGS results they would want about themselves; (2) types of WGS results they would want for their children; and (3) the management of incidental findings in adults and minors in clinical settings. The questionnaire also gathered demographic information about the participants. For nondemographic questions, participants were asked to respond on a 4-point Likert scale ranging from "strongly disagree" to "strongly agree."[8] Although we did not assess participants' baseline knowledge of genetics/genomics, we administered the questionnaire immediately after the educational session about genetics and genomics in order to establish that all participants were exposed to similar information about topics addressed in the survey prior to responding to the questions. For consistency, the same wording, definitions of terms (incidental findings, etc), and examples were used in both the presentation and survey administration.

The survey was administered using Turning Technologies (Turning Technologies LLC, Youngstown, Ohio), which uses PowerPoint-imbedded surveys and enables the collection of anonymous responses through a hand-held device. The questionnaire was read aloud by one of the authors (RV) as participants responded using their hand-held devices, and the anonymous responses were documented immediately. Results for each question were shown to participants after the devices received and tabulated responses from all participants. This study was approved by the Human Research Protections Program, the Institutional Review Board at MCW.

Table 1. Participant Characteristics

Characteristics, N=97	%	(n)
Gender		
Female	97.7	(83)
Male	2.4	(2)
Age		
18-25	1.2	(1)
26-35	16.7	(14)
36-45	23.8	(20)
45-55	27.4	(23)
56 +	31	(26)
Educational Level		
High school diploma or GED	4.8	(4)
Certificate program	43.4	(36)
2-year associate degree	24.1	(20)
Bachelor's degree	24.1	(20)
Master's degree	3.6	(3)
Other advanced degree (MD, JD, PhD)	0	(0)
Length of Time Practicing in Primary Work Role		
Still in training	2.4	(2)
0-5 years	16.7	(14)
6-10 years	27.4	(23)
11-15 years	19.1	(16)
16-20 years	15.5	(13)
21 or more years	19.1	(16)
Number of Children		
0	26.2	(22)
1	16.7	(14)
2	32.1	(27)
3	19.1	(16)
4	1.2	(1)
5 or more	4.8	(4)

Abbreviation = GED, General Educational Development

Statistical Analysis

The survey response data were downloaded from the Turning Technologies software and exported to SPSS Statistics (IBM, Armonk, New York) for statistical analysis. Descriptive statistics were conducted on all survey questions. For the questions with Likert scale responses, "strongly" and "somewhat," categories were combined to result in two categories rather than one for ease of reporting and to be able to compare results with the first administration of the survey and maintain statistical procedural consistency.[8] Valid percentages for each question are reported. (Missing responses are excluded; therefore, response rates vary for each question.) Cross tabulations were conducted to examine differences in responses between categories of respondents, such as age, having children, and wanting one's genome sequenced.

Table 2. Survey Results

Question	Response % (n)
I would want to know about an incidental finding that indicates a genetic association with an:	**Somewhat or Strongly Agree**
Adult-onset disease that is "clinically actionable."	96.5 (82)
Adult-onset disease that is NOT "clinically actionable."	80.7 (67)
Adult-onset disease with uncertain clinical significance.	74.2 (66)
I would want to know about an incidental finding about my child that indicates a genetic association with a/an:	**Somewhat or Strongly Agree**
Childhood-onset disease that is "clinically actionable."	98.8 (82)
Childhood-onset disease that is NOT "clinically actionable."	83.7 (72)
Adult-onset disease that is "clinically actionable."	95.3 (81)
Adult-onset disease that is NOT "clinically actionable."	77.1 (64)
Disease with uncertain clinical significance.	83.3 (70)
In an adult patient: I think an incidental finding should be made available that indicates a genetic association with an:	**Somewhat or Strongly Agree**
Adult-onset disease that is "clinically actionable."	95.3 (82)
Adult-onset disease that is NOT "clinically actionable."	91.7 (77)
In minor (under 18) patient: I think an incidental finding should be made available that indicates a genetic association with a/an:	**Somewhat or Strongly Agree**
Childhood-onset disease that is "clinically actionable."	98.8 (81)
Childhood-onset disease that is NOT "clinically actionable."	91.4 (74)
Adult-onset disease that is "clinically actionable."	94.9 (74)
Adult onset disease that is NOT "clinically actionable."	84.7 (72)

Chi-square and Fisher exact statistical tests were used to ascertain if there were statistically significant differences in responses between groups. Exact *P*-values were calculated; a significance level of ≤ 0.05 was used throughout analysis.

RESULTS

There were a total of 97 participants in the sample. Participants could abstain from answering any questions; therefore, response rates were calculated based on the number of answers provided for each question. See Table 1 for demographic characteristics of the sample and Table 2 for survey questionnaire results. Over two-thirds of respondents (67.6%, n=50) reported wanting their genome sequenced; 24.3% (n=18) did not want their genome sequenced; and 8.1% (n=6) were unsure at the time of the survey. A slight majority of the respondents (56.2%, n=50) strongly or somewhat agreed that they would want their child's genome sequenced.

Overall, there was a reported desire among study participants to receive information about IFs both for themselves and for their children for all categories of findings. These items asked participants to respond to the questions as though they, or their child, were receiving sequencing for a particular diagnostic indication and an "incidental finding" was detected. There were no significant differences in responses about IFs between participants who had children and those who did not. Data for those who strongly or somewhat agreed with the statements are reported in Table 2.

For several questions, there were statistically significant differences in responses between those who indicated that they would want their genome sequenced and those who would not. Nearly three-fourths (72.9%, n = 35) of respondents who would want their genome sequenced agreed or somewhat agreed that they would also want their child's genome sequenced, which was significantly higher than among those respondents who would not want their genome sequenced or were unsure, χ^2 (3, n = 72) = 38.138, $P < .000$. In addition, 89.6% (n = 43) of respondents who would want their genome sequenced strongly or somewhat agreed that they would want to know about an IF regarding an adult-onset disease that was not clinically actionable, which was significantly higher than respondents who did not want their genome sequenced or were unsure, χ^2 (2, n = 71)=10.13, $P = .006$. Moreover, 87.8% (n = 43) strongly or somewhat agreed that they would want to know about an incidental finding with uncertain clinical significance, which was significantly higher than among those who would not want or were unsure about having their genome sequenced, $\chi^2(2, n = 73) = 15.049$, $P = .001$. Slightly over 85% (85.1%, n = 40) strongly or somewhat agreed that they would want to know about an IF in their child related to an adult-onset disease that was not clinically actionable, $\chi^2(2, n = 70) = 6.942$, $P = .031$. Finally, 91.7% (n = 44) of those who would want their genome sequenced strongly or somewhat agreed that they would want to know about an IF in their child with uncertain clinical significance, which was significantly higher than the comparison group, $\chi^2(2, n = 72) = 7.820$, $P = .020$. There were no significant differences in wanting one's genome sequenced in terms of age of participant, number of children, or having children.

DISCUSSION

This is the second time this survey has been used to explore attitudes regarding the return of incidental findings. Unlike the previous administration of this survey, which involved clinical genetics professionals,[8] this study queried participants who did not have special qualifications regarding genetics and whose edu-

cation levels were similar to that of the general Wisconsin public (http://www.census.gov/compendia/statab/2012/tables/12s0233.pdf). Therefore, this study begins to provide some information on the attitudes of a nonspecialist group regarding WGS and receipt of possible "results" of genomic testing.

While the participants in this study were not genetics professionals, answers to many of the questions demonstrate similar agreement/disagreement percentages. Both the expert and nonexpert study participants reported very similar, nearly unanimous desire for the return of adult-onset "clinically actionable" results for themselves (~96%) and "clinically actionable" childhood-onset conditions for children (~99%). This subset of the lay population was considerably more interested in receiving all types of results for both themselves and their children. Regardless of whether a disease-causing variant was actionable, the majority of participants in this study (>74%) reported that they would want to be informed of findings. This is in contrast to the genetic professionals' survey results, wherein less than half of the respondents reported a desire to know about nonactionable findings. There could be several factors contributing to this contrast, including divergent baseline knowledge and familiarity with potential legal and financial implications of genetics testing (ie, the Genetic Information Nondescrimination Act [GINA] and the Health Insurance Portability and Accountability Act [HIPAA]). Although beyond the scope of the introductory lecture and assessment of this survey, these considerations provide future direction for investigation and should be considered in the context of this comparison. The potential lack of knowledge about this legislation among this study's participants may have contributed to their higher interest in receiving results that may be nonactionable or have uncertain clinical significance.

Interestingly, when questions moved toward the return of results, participants who reported that they would not choose to undergo WGS still indicated they would want to receive the results. Understanding what is driving a desire for disclosure of results once known, when not interested initially in pursuing the technology that would provide those results, requires more study. Once the leap is made (in our hypothetical scenarios) to the situation wherein testing is complete and findings are available, most people do not appear to want those findings withheld. It is possible that—similar to other qualitative studies involving lay populations[21]—these results may represent a desire for involvement in decision making and a resistance to others knowing something they do not. Preferences or opinions are relevant to the discussion; however, consideration must be made for emotion and influence of perception of fact associated with such inquiry. Attempts to exclude patients/parents from taking part in the decision-making process may not be supported by the population itself.

In this study, interest in testing for oneself correlates with a strong reported desire to receive genetic findings for both oneself and children, regardless of potential actionability related to the finding. It is notable that a very high percentage of participants reported a desire for return of results, even when the results have uncertain clinical significance or are not clinically actionable. In contrast, the genetic professional population previously studied was considerably more opposed to the return of such results.[8]

Study Limitations

This study points to differences in attitudes regarding incidental findings between medical and nonmedical audiences; however, there are several limitations. First, the participants may not be representative of a truly "lay" audience given their exposure to medical concepts through their work with medical records. Thus, the findings are not generalizable to other nonmedical populations, and they may be biased because these nongenetics professionals work in an academic medical center where innovative tests and therapies are commonly introduced. Most participants (97.7%) were women; thus, the findings are largely representative of female perspectives on IFs.

The use of Turning Technologies as a data collection mechanism may have limited the degree of participation among survey participants who are not familiar with or comfortable using new technologies.

In addition, this study is limited in the scope of statistical analysis that could be performed due to the overall small sample size and variable number of responses per question. Although we assessed how many children participants had, we did not explore what type of parent (ie, parenting style, characteristics) participants see themselves as being, which could influence their responses in terms of their desires for IF reports for their children.[22,23]

This type of attitudinal survey is not designed specifically to explore participant knowledge, understanding, or thought processes prior to their selection of particular answers. It is noteworthy that this study lacked information about the participants' knowledge and comprehension of factors that influence decision-making about IFs, such as a full grasp of the risks (including the limitations of current privacy regulatory protections) and benefits of genomic testing in various contexts. Methodologies allowing for more in-depth exploration of motivation, such as open-ended and cognitive interview, will be needed to better assess this understanding as well as the disconnect between the lack of desire for the test, but a largely congruent desire for the test result. In addition, the results of this survey are based on hypothetical questions and may not represent how participants would act in the future.

CONCLUSION

There are many clinics and providers that offer a patient-centered approach to diagnostics and medical management. Personalized care has been an emerging theme among institutions across the country. The popularity of direct-to-consumer genetic testing

suggests that some patients/consumers desire a certain level of control or decision-making capacity in their health care diagnosis and management. This is not to say that patients should have the only opinion that matters during the decision-making and policy consideration time; rather, it acknowledges that they are key stakeholders in the genomics era. Further investigation and research is needed among a broader population to increase generalizability; however, this study offers a snapshot of opinions beyond the genetics community. While it is important to acknowledge that empirical data regarding preferences/attitudes/opinions are not in themselves sufficient to direct policy,[24] overwhelming public/professional sentiment that contradicts policy should be a flag for a need to further discuss the basis upon which policy has been set. In order to avoid such a situation, empirical data regarding preferences/attitudes/opinions provide useful contextualization. In the absence of other data, we recommend that clinical discussions and decisions about the return of incidental findings following genome sequencing continue to take account of patient preferences regarding the receipt of such results.

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A One-to-One Mentoring Support Service for Breast Cancer Survivors

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ABSTRACT

Purpose: ABCD: After Breast Cancer Diagnosis (ABCD) is a Wisconsin-based mentoring service that pairs breast cancer survivors with women recently diagnosed with breast cancer. Since 1999, ABCD has trained volunteers to provide personalized information and emotional support. This review describes participants' perceptions of this survivorship program and its utility for breast cancer patients.

Methods: ABCD conducted 3 "program effectiveness" surveys between 2002 and 2006. Surveys were conducted over the telephone and used a 5-point Likert scale to elicit evaluations of the organization, mentors, resources, and other program dimensions.

Results: Survey results indicate that this model is a successful resource that could be replicated for breast cancer survivors nationally. Respondents were especially satisfied with the helpfulness of the program for them and their families, mentor confidentiality, and emotional support. Areas for improvement focused on mentee familiarity with the ABCD website and helpline and improvement in mentor knowledge. Approximately 60% of respondents would consider becoming mentors.

Conclusion: ABCD is a positive and successful program with consistent participant satisfaction. The program has expanded nationally to address the needs of survivors. This model could be further replicated to provide support to survivors, family, and friends at no cost.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women.[1] Because of screening and early detection, as well as improvements in treatment options, many women are living longer with breast cancer or are being cured entirely. According to the Centers for Disease Control, the number of cancer survivors in the United States has increased from 9.8 million in 2001 to 11.7 million in 2007, including more than 2.5 million breast cancer survivors.[2] An estimated 64.8% of cancer survivors live longer than 5 years after their cancer diagnosis and a large portion of these patients are breast cancer survivors.[2]

Cancer survivorship, defined as the time from diagnosis until the end of life,[3] was identified by the Institute of Medicine in 2006 as a distinct phase of the cancer journey that has been neglected in advocacy, education, clinical practice, and research.[4] Cancer survivors face unique physical and psychosocial challenges across the life course, including psychological distress, sexual dysfunction, infertility, impaired organ function, cosmetic changes, and limitations in mobility, communication, and cognition, among others.[4] In the face of these challenges, it is now widely accepted that survivors benefit from emotional and informational support throughout the cancer journey.[5-8] The documented benefits of participation in cancer support groups range from enhanced quality of life to prolonged survival,[9,10] indicating that support-based programs may be an important resource for addressing the needs of cancer survivors.

There is a growing interest in volunteer-based programs in particular because of their shared-experience element, accessibility, and cost effectiveness. According to a recent systematic review, there is a paucity of literature on volunteer-based support programs for people with cancer.[11] While evidence does suggest that most volunteer-based support programs are beneficial for participants, volunteer programs often face challenges with sustainability, as well as growth and application in multiple populations.[11] Here we present the case of ABCD: After Breast Cancer Diagnosis (ABCD), a structured volunteer program that has been in place for 15 years and recently has expanded to have a national presence.

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Table 1. Sample Survey Questions and Mean Likert Scale Responses

ABCD (After Breast Cancer Diagnosis) Organization	2006 n = 139	2004 n = 92	2002 n = 53
ABCD is a reliable source for support	4.55	4.67	4.33
ABCD is a reliable source for information	4.37	4.47	4.09
It is easy to contact someone at ABCD	4.65	4.67	4.47
One-to-one contact is valuable	4.65	4.74	4.62
The ABCD organization is responsive in a timely manner	4.68	4.68	4.60
The ABCD program has helped me	4.41	4.47	—
The ABCD program has helped my family	3.84	—	—
Overall evaluation of ABCD	4.58	4.56	4.43
ABCD Mentors			
My ABCD mentor was well informed	4.48	4.52	4.31
My ABCD mentor was responsive to my questions/concerns	4.52	4.66	4.51
I felt comfortable sharing personal information with my mentor	4.46	4.55	4.41
My ABCD mentor provided emotional support	4.40	4.38	4.09
My ABCD mentor helped me get the additional breast cancer information I need	3.83	4.15	—
I trust my discussions with my mentor were kept completely confidential	4.77	4.74	4.74
Overall evaluation of ABCD mentor	4.35	4.41	4.31
ABCD Resources			
Not at all familiar with ABCD website	61%	65%	77%
Not at all familiar with ABCD helpline	38%	35%	44%

Mean Likert scale rating for all respondents, where 1 indicates "Strongly Disagree" and 5 indicates "Strongly Agree."

METHODS

Program Description

ABCD is a Wisconsin-based organization originally established to meet the needs of breast cancer survivors and their families in Eastern Wisconsin (http://www.abcdbreastcancersupport.org/). While ABCD is based in southeast Wisconsin and actively serves all of Wisconsin's 72 counties, its services are now available in communities nationwide. Milwaukee County, home to the organization's headquarters, has the highest rates of breast cancer in Wisconsin and includes the state's most socioeconomically diverse population.

Breast cancer survivors who are at least 1 year past the completion of treatment or people who have had experience with breast cancer with family members or friends can volunteer to serve as mentors with ABCD. New volunteers complete 12 hours of training, with instruction on breast cancer diagnosis, treatment options, psychosocial issues, resources for survivors, and health information privacy. The goal of the peer support is to decrease the survivor's sense of isolation, increase knowledge about the breast cancer experience, introduce possible coping strategies, and provide a sense of hope.

Program Process

ABCD staff pair mentors with mentees in a deliberate process tailored to the mentee's needs. A mentee who is seeking mentorship works with ABCD staff to complete an intake form that queries relevant information on demographics, health, and cancer status.

The mentor and mentee usually first communicate by telephone, and if they wish to continue the relationship, continued contact can be initiated. Matches are afforded a great deal of autonomy, with no direct supervision and no predetermined end to the relationship. ABCD does, however, conduct regular check-ins with both mentors and mentees to assess their satisfaction with the match and offer additional support where needed.

Survey and Data Collection

ABCD began matching survivors and mentors in September 1999. Since then, with the assistance of an independent marketing and survey firm, ABCD conducted 3 "program effectiveness" surveys, in 2002, 2004, and most recently in 2006. Survey questionnaires, designed collaboratively by the independent firm and members of the ABCD program committee, consisted of 8 questions about the ABCD organization, 12 questions about mentor services, and 9 questions addressing resources and other topics (Table 1). ABCD volunteers administered the survey as a 5-minute telephone interview, conducted in English. Mentors who volunteered as survey administrators did not contact their own mentees. Respondents were asked to evaluate the attributes of ABCD on a 5-point Likert scale, from 1 (strongly disagree) to 5 (strongly agree). Participants were informed that an independent marketing firm was assisting in data collection. Participants did not receive any incentive for their participation. The independent firm compiled and analyzed de-identified data for ABCD. With all data de-identified, this work was exempted from review by our institutional review board (IRB).

Analysis

We provide descriptive statistics to characterize the survey cohort. The independent firm calculated mean scores for each of the Likert-scaled questions. Chi-square tests were performed to identify significant associations between survey year and characteristics of the match. Number of surveys conducted was estimated from program participation levels for 2002 and 2004.

RESULTS

Survey Respondents

Analysis of the questionnaires was conducted to evaluate the respondent perceptions of the program and to identify areas in need of improvement. In the most recent survey, volunteers telephoned all survivors who had received mentoring services during the prior 2 years (N=265). One hundred thirty-nine women completed at least 75% of the questionnaire, for a participation rate of 52%. This participation rate is up from 45% and 25% in

the previous 2 surveys (Table 2).

Over half of respondents learned about ABCD through health care settings, either directly from their physician/oncologist (23%), or nurse (12%), or from the hospital or clinic (22%). Others learned about the program from a friend or relative, through their church, or at an ABCD fundraising event. Estimated length of relationship with the mentor was asked of participants during the time period of most active treatments (1 year). For 41% of respondents, the mentor relationship lasted from 6 months to 1 year, an increase compared to the previous 2 surveys (33% and 17% respectively). Only 8% estimated the relationship lasted less than 3 months ($P = 0.003$) (Figure 1). The majority of respondents (71%) were involved with only 1 mentor while they received services at ABCD. The number of contacts between the mentor and survivor increased significantly over the years. In 2006, 23% of respondents reported they had had more than 15 contacts with their mentor throughout the relationship, compared to 6% and 16% in 2002 and 2004, respectively ($P = 0.02$) (Figure 2). Nearly all respondents (96%) would refer another breast cancer survivor to ABCD and 60% would consider becoming mentors themselves.

In the most recent survey, respondents gave a mean Likert rating of 4.41 in response to the statement: "The ABCD program has helped me." Respondents gave a mean Likert rating of 3.84 in response to the statement: "The ABCD program has helped my family" (Table 1). When asked about their familiarity with ABCD resources, 61% of respondents were not familiar with the ABCD website and 38% were not familiar with the ABCD helpline (Table 1). The statement with which respondents most agreed (mean Likert rating of 4.77) was: "I trust my discussions with my mentor were kept completely confidential" (Table 1). The lowest mean Likert score (3.83) came in response to the statement: "My ABCD mentor helped me get the additional breast cancer information I need."

Table 2. Survivor Demographics Data

	2005-2006	2003-2004	2000-2002
Number of Survivors/Mentors[a]	**265**	**203**	**208**
Number of matches	303	233	247
Demographics of Patients/Survivors Receiving Matches			
Unknown	18	13	9
African American	27	18	8
Caucasian	254	169	191
Hispanic	4	3	—
Survey participation	52%	45%	25%

[a]The number of participants each year is less than the number of matches, as multiple participants (mentors) have multiple matches.

Figure 1. Estimated Length of Relationship with Mentor

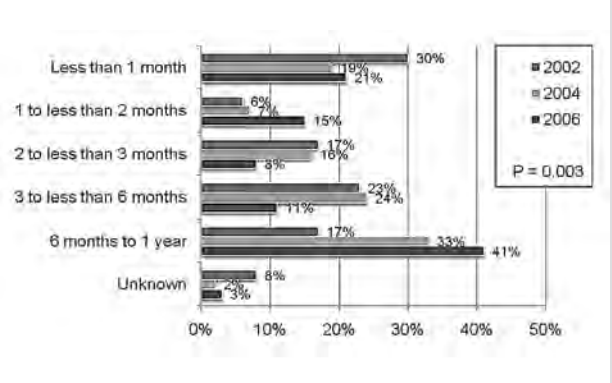
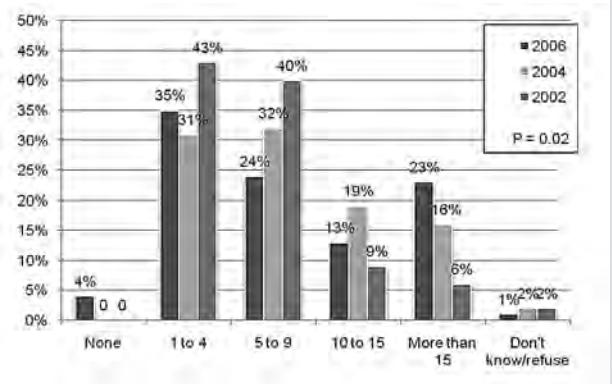


Figure 2. Estimated Number of Contacts with the Mentor



DISCUSSION

This report from 3 surveys of a Midwest breast cancer support group demonstrates that survivors and their families and friends are very satisfied with ABCD's support services, and that the level of satisfaction has remained stable over the 3 surveyed time periods. More mentoring relationships are lasting longer and the number of contacts between mentors and mentees have increased over time. These findings reinforce the value of the program to survivors. Over 70% of respondents reported that they had contact with only 1 mentor, suggesting that ABCD's efforts to appropriately pair matches are largely successful. Finally, participation in the program has increased over time and has expanded nationally. This model could be replicated for breast cancer survivors in other communities.

Social support resources for breast cancer patients have been evaluated extensively in the existing literature.[12] Programs that have been piloted and implemented include group mentoring[9,13] and one-to-one mentoring in person,[11] via telephone,[7] or over the Internet.[14] In some programs, such as Reach to Recovery, mentors are fellow breast cancer survivors,[11] while other programs offer mentorship by someone trained in a health care field such as a registered nurse, or someone trained in counseling such as a psychologist.[6] Though it is clear that each of these modalities

can provide benefit to the survivor, there is no data to suggest a benefit to using 1 modality over another.[12] Our study adds to the literature by describing a model for a successful one-to-one mentoring program that can provide support to women diagnosed with breast cancer.

Many survivorship programs serve women with breast cancer, but the context of that service is key; it is important that programs provide adequate support through a forum that is safe and educational. This point is especially important in the light of evidence that some programs actually can cause harm. For example, 1 randomized controlled trial of peer-to-peer interactions in an unstructured, unmediated online format found that participants in the experimental arm experienced decreased quality of life and increased stress compared to participants in the control arm.[13] Some evidence suggests that the time spent screening, training, supervising, and retraining mentors may be a crucial factor in the success of the mentor-survivor relationship.[7] ABCD provides 12 hours of training for potential mentors, followed by a post-training evaluation to assess the readiness of potential mentors. In addition, ABCD offers continuing education opportunities 3 to 4 times a year to keep mentors informed about available resources, new or different medical treatments, and coping strategies for psychosocial issues. This analysis demonstrates consistently across all 3 survey periods that mentees have reported: that ABCD is a reliable source of support (mean Likert ratings: 4.33 [2002], 4.67 [2004], 4.55 [2006]); and that their mentor has provided them with emotional support (mean Likert ratings: 4.09 [2002], 4.38 [2004], and 4.40 [2006]).

While all mean Likert ratings were above 3.5, in the future ABCD may focus additional efforts on components of the program that were not rated as highly as others such as training mentors to more effectively provide information to mentees, assessing the support needs of participants' families, and raising awareness of the website and expanded helpline. Although we describe a successful peer support program for breast cancer survivors, there are some limitations with the data. First, the survey initially was designed with the goal of expanding marketing of ABCD. While the data speak to respondents' impressions of the program, future surveys designed by experts in health program evaluation may provide additional relevant information. Second, while demographic information is available for all survivors involved with ABCD, we do not have specific demographic data for the subset of women who responded to the survey. While the response rate to these surveys has increased significantly over time, there is still the possibility for selection bias, where participants who are most and least happy with ABCD's services may be most likely to respond. The survey was administered only in English, which excluded participants who were not comfortable communicating in English. Since the last survey was conducted in 2006, ABCD has taken steps to address this limitation by training and matching several mentors who are bilingual in English and Spanish and can provide services to Spanish-speaking survivors. Finally, ABCD does not have records of the total number of survivors invited to participate in the first 2 surveys. Instead, they estimated the numbers, and in turn the response rates, based on their mailing lists.

Since the completion of the 2006 survey, a follow-up survey has not been conducted due to programmatic changes and the rapid expansion of the program. In 2012, ABCD expanded its helpline staff, bringing on volunteers and staff members from the recently closed Y-ME, one of the oldest breast cancer support organizations in the world. ABCD's goals are to eventually further expand its helpline into a 24/7, survivor-staffed resource serving all 50 states and to increase the number of mentee-mentor matches.

ABCD currently is designing a new survey as part of a prospective study to evaluate the experiences of both mentees and mentors. This kind of ongoing, systematic evaluation is crucial as ABCD expands its reach in the United States. Records from 2013 identify 531 matches for which 1593 one-to-one services were provided. ABCD now has mentors and matches throughout the nation, with particularly strong mentor cohorts and programming arms in Washington DC, Chicago, Miami, San Antonio, Phoenix, and southern California.

In summary, surveys of ABCD participants from 3 time points indicate that women appreciate the support services provided by ABCD and believe ABCD programming is an effective resource for survivorship care. Meanwhile, ABCD's expansion and continued growth since the last survey suggests that the ABCD mentoring program is a replicable model for one-to-one mentoring support services. As the numbers of breast cancer survivors grow and as breast cancer treatments continue to improve and become more complex, it is likely that there will be growing demands for information and support among this population. ABCD is poised to contribute to meeting this demand; the organization serves as a model program for providing enduring and effective peer support to breast cancer survivors using local resources at no cost to the survivor.

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Identifying Opportunities to Improve Aspirin Utilization for the Primary Prevention of Cardiovascular Disease in a Regional Health Care System

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ABSTRACT

Objective: Aspirin is an important part of primary cardiovascular disease prevention, but little is known about aspirin use patterns in regional health care systems. This study used electronic health records from Marshfield Clinic to identify demographic, geographic, and clinical predictors of aspirin utilization in central Wisconsin adults without cardiovascular disease.

Methods: A cross-sectional design was employed using 2010-2012 data from patients in the Marshfield Epidemiologic Study Area. Individuals who took aspirin-containing medication daily or every other day were considered regular aspirin users. There were a total of 6678 adults in the target region who were clinically indicated for aspirin therapy for primary cardiovascular disease prevention, per national guidelines.

Results: Aspirin was generally underutilized in this population, with 35% of all clinically indicated adults taking it regularly. Adjusted models found that individuals who were younger, female, not covered by health insurance, did not visit a medical provider regularly, smokers, were not obese, or did not have diabetes were least likely to take aspirin. In addition, there was some local variation in that aspirin use was less common in northeastern communities within the regional service area.

Conclusion: Several aspirin use disparities were identified in central Wisconsin adults without cardiovascular disease, with particularly low utilization observed in those without diabetes and/or without regular physician contact. Methods of using electronic health records to conduct primary care surveillance as outlined here can be adopted by other large health care systems in the state to optimize future cardiovascular disease prevention initiatives.

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CME available. See page 196 for more information.

INTRODUCTION

Cardiovascular disease (CVD) is the principle driver of mortality in the United States.[1] Despite steady reductions in both incidence and mortality[2] over recent decades, the overall prevalence of CVD is expected to rise due to an aging population and increased diabetes comorbidities.[3] Without further reductions in new CVD cases, the health care resources required to manage CVD are feared to outstrip financial capacity. CVD preventive medical care focuses on risk factor modification, namely control of elevated blood pressure and lipids.[4] Control of platelet aggregation via low-dose aspirin is also important for those at high risk of experiencing a CVD event.[5,6] Though aspirin therapy for primary CVD prevention remains controversial,[7,8] meta-analytic evidence suggests that it lowers CVD risk by nearly 15% over 7 years.[9]

Aspirin use has been increasing in the United States overall,[10,11] with at least 41% of all US adults over age 40 now taking it regularly.[12] Aspirin is routinely recommended and well utilized in Wisconsin's secondary prevention population with active CVD,[13] but pharmacoepidemiologic research on aspirin use in primary CVD prevention populations is much less common. The most recent statewide research found that about one-third of Wisconsin adults age 35 to 74 years without CVD or diabetes are clinically indicated for aspirin therapy, and of these, just 31% report taking aspirin regularly.[14] Consistent with other previous research, Wisconsinites in older age groups are most likely to use aspirin.

State- and national-level studies are helpful in detecting broad trends in aspirin utilization, but they are less relevant at local levels where targeted health initiatives are more likely to occur. The recent widespread adoption of electronic health records

(EHR) by large health care delivery systems presents opportunities to reuse clinical data for community-level epidemiologic research. There are at least some burgeoning EHR models that can inform regional CVD risk factor surveillance and pharmacoepidemiology,[15-17] but none have specifically examined aspirin at a population level. In order to help regional health care systems leverage their own data to direct primary care initiatives toward patients most likely to benefit, this is an important research gap to address. The purpose of this study was to characterize regular aspirin use in central Wisconsin adults without CVD (who are clinically indicated for aspirin), as well as to identify regional demographic and clinical disparities in aspirin use.

METHODS

Design and Setting

A cross-sectional analysis was performed using data extracted from the Marshfield Clinic research data warehouse, which stores medical and administrative information captured within the system EHR during clinical encounters. The target population was the central portion of the Marshfield Epidemiologic Study Area (MESA). As described in more detail elsewhere,[18] MESA is a regional population-based health research resource that includes patients (and their associated family members) who received care from Marshfield Clinic and reside in 1 of the ZIP codes that surround the primary service area in central Wisconsin. This region is predominantly rural, covering over 1000 square miles, with about 56,000 total residents who receive over 90% of their inpatient and outpatient health care from Marshfield Clinic.[19]

Sample

All data were collected over a 3-year timeframe between January 1, 2010 and December 31, 2012. Eligibility criteria for this analysis were, as of December 31, 2012: (1) current living status in MESA Central, (2) ≥ 1 ambulatory encounter with a Marshfield Clinic medical provider during the study timeframe, (3) no personal history of ischemic vascular disease (ie, myocardial infarction, angina, ischemic stroke—specific diagnostic codes available upon request), and (4) clinically indicated for aspirin therapy for primary CVD prevention, per the US Preventive Services Task Force (USPSTF)[6] and, for those with diabetes, the American Diabetes Association (ADA)[20] guidelines as detailed below. Because this was a retrospective analysis of existing health care data, the study was approved by the Marshfield Clinic Institutional Review Board (IRB) with a waiver of informed consent.

Indication for Aspirin Therapy

The clinical indication for aspirin therapy for primary CVD prevention was determined for all subjects based on current USPSTF[6] and ADA[20] guidelines. Among patients without diabetes, those indicated for aspirin included men in the following age-risk categories for coronary heart disease: 45 to 59 years and ≥ 4% risk, 60 to 69 years and ≥ 9% risk, and 70 to 79 years and ≥ 12% risk; and women in the following age-risk categories for stroke: 55 to 59 years and ≥ 3% risk, 60 to 69 years and ≥ 8% risk, and 70 to 79 years and ≥ 11% risk. For patients with diabetes, men and women with ≥ 10% risk of CVD are indicated for aspirin therapy. Assuming no contraindications, the USPSTF and ADA recommend aspirin in these groups because the probability of cardioprotection outweighs that of major gastrointestinal or intracranial hemorrhage. A 10-year risk of CVD, coronary heart disease, or stroke was calculated for each individual using the global CVD risk equation from the Framingham Heart Study.[21] This method estimates the risk of all CVD using information on age, sex, smoking, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and diabetes. The global CVD risk score can then be multiplied by a correction factor to determine the specific 10-year risk for coronary heart disease (for men without diabetes) and stroke (for women without diabetes). Those with a known aspirin contraindication were not indicated for aspirin therapy under the USPSTF and ADA guidelines. Comprehensive assessment of aspirin contraindications using administrative data is not well established, however, because clinical judgment is often needed to determine the severity of a given health condition in this context. As such, only select aspirin contraindicative diagnostic codes were screened for in the EHR based on previous recommendations.[22,23] These included a previous history of a salicylate adverse events, gastrointestinal bleeding, intracranial bleeding, or severe liver disease. Other, more relative potential contraindications such as concurrent use of anticoagulants or nonsteroidal anti-inflammatory drugs (NSAIDS), poorly controlled hypertension, and/or gastroesophogeal reflux were not considered in this study.

Measures

Outcome

Based on previous state-level methods developed for standard health care quality reporting,[13,22] the primary outcome was regular use of aspirin-containing medication. Known initiation/discontinuation dates, dose, and frequency of all patient reported medications were collected in patient interviews conducted as part of the routine workflow during Marshfield Clinic encounters and stored in the system EHR. There are no known objective validation studies of EHR-derived aspirin use, but 1 previous study found strong agreement between manual chart-audited and EHR-automated text-derived aspirin use in adults with diabetes.[16] Another study showed strong agreement between self-reported regular aspirin use and a blood byproduct of salicylates.[24]

In this study, EHR-derived medications were first linked to the therapeutic classification system of the American Society of

Table 1. Descriptive Characteristics, Stratified by Regular Aspirin Use

Characteristics	Regular Aspirin Use n = 2,346	Irregular or No Aspirin Use n = 4,332	*p*
Age (y)	61.6 ±8.5	56.5 ±8.0	<0.001
Sex			
Female	339 (14%)	364 (8%)	<0.001
Male	2,007 (86%)	3,968 (92%)	
Race/Ethnicity			
White, non-Hispanic	2,253 (96%)	4,078 (94%)	0.001
Non-white, non-Hispanic	35 (1%)	64 (1%)	
Hispanic	26 (1%)	73 (2%)	
Unknown	32 (1%)	117 (3%)	
Health Insurance			
Commercial only	1,456 (62%)	3,022 (70%)	<0.001
Public assisted	828 (35%)	1,042 (24%)	
None	62 (3%)	268 (6%)	
Residential Community (ZIP code)			
Dorchester	52 (2%)	121 (3%)	0.097
Abbotsford	108 (5%)	200 (5%)	
Colby	113 (5%)	238 (5%)	
Stratford	202 (9%)	434 (10%)	
Unity	62 (3%)	79 (2%)	
Spencer	172 (7%)	303 (7%)	
Hewitt	45 (2%)	73 (2%)	
Auburndale	96 (4%)	207 (5%)	
Arpin	78 (3%)	166 (4%)	
Milladore	50 (2%)	81 (2%)	
Chili	45 (2%)	100 (2%)	
Pittsville	133 (6%)	217 (5%)	
Marshfield	1,190 (51%)	2,113 (49%)	
Number of Ambulatory Visits in the Past 3 Years	12.4 ±9.8	9.0 ±8.4	<0.001
Smoking			
Current	336 (14%)	1,000 (23%)	<0.001
Former	930 (40%)	1,322 (31%)	
Never	1,080 (46%)	2,010 (46%)	
Body Mass Index (kg/m2)	32.4 ±6.7	30.9 ±6.4	<0.001
Diabetes			
Yes	755 (32%)	559 (13%)	<0.001
No	1,591 (68%)	3,773 (87%)	

Table shows descriptive characteristics of central Wisconsin adults who were clinically indicated for aspirin therapy for the primary prevention of cardiovascular disease in 2012, stratified by regular aspirin use.
All values are reported as mean ±standard deviation or frequency (% of total).
P-value corresponds to the difference between the 2 groups.

Health-System Pharmacists.[25] All salicylate class medications were reviewed and the generic names of aspirin-containing medications screened for during data extraction, including aspirin, aspirin/calcium carb, aspirin/magnesium carb/al aminoacet, aspirin/magnesium hydrox/al hydrox, and aspirin/calcium carb/magnesium/al hydrox. Per standard practice,[22] combined aspirin-narcotic medications (eg, aspirin plus codeine) were not considered due to the transient nature of such therapies. Also, other prescription antiplatelet agents such as clopidogrel were not considered as they typically are reserved only for secondary CVD prevention. Individuals who took aspirin-containing medication daily or every other day at their most recent encounter within the study timeframe were considered current regular aspirin users. Participants who did not take (or discontinued) aspirin at their most recent encounter, took aspirin as needed (PRN), or otherwise took aspirin less frequently than every other day were considered irregular aspirin users. Aspirin dose was reported descriptively where available, but could not be considered in the outcome definition due to incomplete data.

Exposures.
Several exposures were considered to identify the best independent predictors of regular aspirin use. These included age, sex, race/ethnicity, health insurance status, residential community, number of ambulatory care encounters over the previous 3 years, smoking, body mass index (BMI), and diabetes. Community was based on the ZIP code of residence within MESA. BMI was calculated as weight in kg divided by height in meters squared. Diabetes was established by the presence of ≥ 2 diagnostic code in 250.xxx occurring before December 31, 2012. All clinical variables were collected by trained staff following standard Marshfield Clinic office-based physical exam and laboratory procedures.

Analyses
All analytical procedures were conducted with SAS Version 9.3 (SAS Institute, Cary, North Carolina). For individuals with missing total or HDL cholesterol, the 10-year CVD risk estimate was calculated using body mass index (BMI) in place of blood lipids, per methods outlined by D'Agostino and colleagues.[21] This method provides a reasonable approximation of CVD risk in the absence of laboratory values. Univariate and multivariable logistic regression was used to examine the association between all exposures and regular aspirin use. An initial multicollinearity check between exposures found no issues, thus all exposures were considered simultaneously in a fully adjusted model. Given the exploratory nature of this analysis, no model reduction techniques were applied. Also, because there is near complete capture of medical care data within the target MESA population, no sample weighting techniques were used.

RESULTS
There were 6,678 individuals identified as clinically indicated for aspirin therapy and meeting all study eligibility criteria. Descriptive characteristics of the analytical sample are outlined in Table 1. As expected, the sample was predominantly male and non-Hispanic white, with the majority residing in the Marshfield community. There were 2,346 (35%) individuals who took aspirin regularly. Among regular aspirin users, 98% indicated daily use. Full aspirin dose information was available only on 530 aspi-

rin users, with an average daily dose of 81mg being most common (77%), followed by ≥325 mg (21%) and 162 mg (2%).

All exposures except residential community were significantly associated with aspirin use in unadjusted models (Table 1). The fully adjusted multivariable model found that adults who were older, male, commercially insured, visited a medical provider regularly, were nonsmokers, had a higher BMI, or had diabetes had significantly higher odds of aspirin use (Table 2). Residential community was modestly associated with aspirin use (Figure). After adjustment for other exposures, rates of aspirin utilization by community ranged from a low of 29% in Dorchester to a high of 45% in Unity. A sensitivity analysis also was conducted using residential census tract (in lieu of ZIP code) in order to view local variation at a more granular level. Parameter estimates from this analysis were very similar to those observed in the main findings (results not shown).

Table 2. Multivariable Association Between Patient Exposures and Regular Aspirin Use

Exposures	Regular Aspirin Use (Yes vs No)	
Age (y)	1.07 (1.06, 1.08)	*P*<0.001
Sex		
Female vs male	0.56 (0.45, 0.68)	*P*<0.001
Race/Ethnicity		
Non-white, non-Hispanic vs white, non-Hispanic	1.26 (0.81, 1.97)	*P*=0.307
Hispanic vs white, non-Hispanic	0.72 (0.44, 1.17)	*P*=0.185
Unknown vs white, non-Hispanic	0.73 (0.48, 1.11)	*P*=0.142
Health Insurance		
Publicly insured vs commercially insured	0.72 (0.63, 0.83)	*P*<0.001
Not insured vs commercially insured	0.62 (0.46, 0.83)	*P*=0.001
Residential Community		
Dorchester vs Marshfield	0.77 (0.54, 1.11)	*P*=0.168
Abbotsford vs Marshfield	0.88 (0.68, 1.15)	*P*=0.345
Colby vs Marshfield	0.85 (0.66, 1.09)	*P*=0.200
Stratford vs Marshfield	0.85 (0.70, 1.04)	*P*=0.109
Unity vs Marshfield	1.55 (1.08, 2.23)	*P*=0.018
Spencer vs Marshfield	1.01 (0.81, 1.25)	*P*=0.952
Hewitt vs Marshfield	1.19 (0.80, 1.78)	*P*=0.395
Auburndale vs Marshfield	0.86 (0.66, 1.13)	*P*=0.277
Arpin vs Marshfield	0.93 (0.69, 1.25)	*P*=0.625
Milladore vs Marshfield	1.00 (0.68, 1.48)	*P*=0.982
Chili vs Marshfield	0.91 (0.62, 1.33)	*P*=0.628
Pittsville vs Marshfield	1.03 (0.81, 1.32)	*P*=0.812
Number of Ambulatory Visits in the Past 3 Years	1.02 (1.01, 1.03)	*P*<0.001
Smoking		
Current vs former or never	0.80 (0.69, 0.93)	*P*=0.003
Body Mass Index (kg/m2)	1.02 (1.01, 1.03)	*P*<0.001
Diabetes		
Yes vs no	2.41 (2.05, 2.82)	*P*<0.001

Table shows multivariable association between patient exposures and regular aspirin use among central Wisconsin adults who were clinically indicated for aspirin therapy for the primary prevention of cardiovascular disease (N = 6678). Values are reported as odds ratio (95% confidence interval) of regular aspirin use. Values less than 1 indicate that as the exposure variable increased (or relative to the reference category for categorical exposures), the odds of aspirin use decreased.

DISCUSSION

Aspirin is underutilized in central Wisconsin, with 35% of adults clinically indicated to take it for primary CVD prevention actually doing so. Adjusted models found that patients who were younger, female, not covered by health insurance, did not visit a medical provider regularly, smokers, were not obese, or did not have diabetes were least likely to take aspirin. Race had limited influence on aspirin use, unlike 1 other study.[11] Otherwise demographic patterns of aspirin use in this study were largely consistent with other previous findings,[10-12] with the overall rate of aspirin use in this study area slightly higher than that observed statewide in 2008-2010.[14]

Clinical factors were notably strong markers of aspirin use in this study. In particular, adults with diabetes had 2.4 times greater odds of taking aspirin relative to those without. In addition, those with private health insurance and who visited the clinic frequently were much more apt to take aspirin. Taken collectively, such factors underscore previous observations that, according to patients, a physician conversation where aspirin is recommended is the most motivating factor for taking aspirin regularly.[12] It seems logical to conclude that patients who are clinically identified as being in poor health (eg, diabetes, obese) and have reasonable access to and utilization of health care (eg, insured, regular physician visits) are more likely to receive such medical advice relative to healthy young adults or those without health insurance who cannot visit the clinic often.

There also was a modest degree of local variation in that several communities north and east of the main Marshfield Clinic campus were least likely to take aspirin. Reasons for this were unclear and did not obviously track with socioeconomic factors. US census data indicate that education and income levels, as well as professional-oriented occupations predictably drop in all directions further away from the population center of Marshfield. Distance from medical care also did not appear to be a strong factor as has been observed in some previous regional research on care for other health conditions.[26] In addition to the main central clinic in Marshfield, there are 2 satellite clinics that deliver primary care in the northern communities, which serve the lowest aspirin use areas. This may present opportunities to focus specific primary care outreach efforts in those locations in order to improve rates of aspirin use across MESA.

Measurement bias was the main study limitation in that aspirin use was reported during patient interviews as part of usual care and precise dosage information was often lacking, presumably because it could not be recalled by patients. Validation studies are scarce on self-reported aspirin use, but indicate generally good

Figure. Prevalence of Regular Aspirin Use

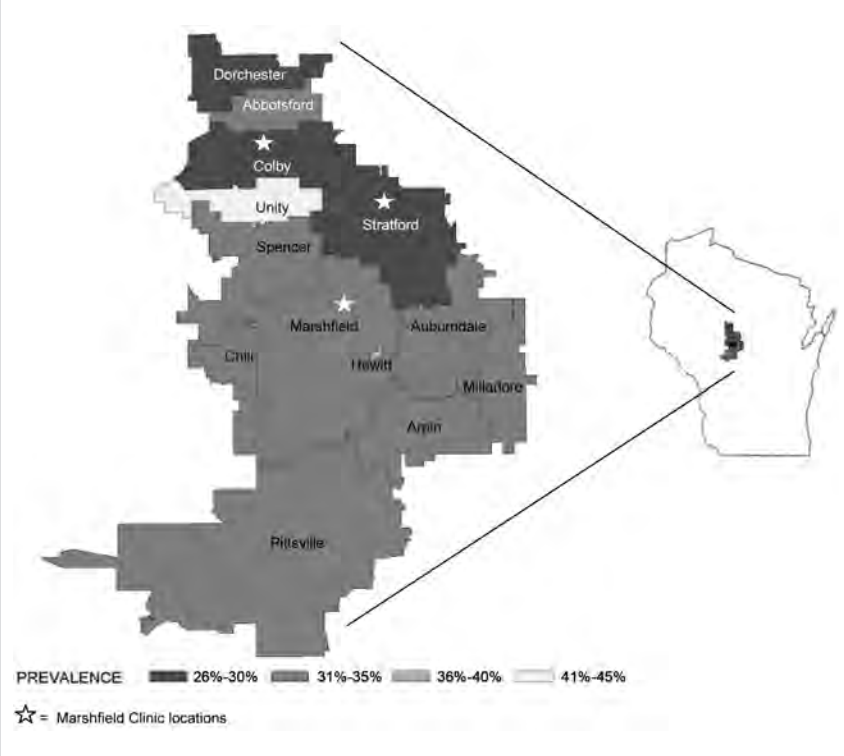

Figure shows regular aspirin use among adults clinically indicated for aspirin for primary cardiovascular disease prevention, stratified by residential community within the Marshfield Epidemiologic Study Area.

accuracy and correlation with biomarkers.[24] The timing of the aspirin assessment at the most recent visit also may be an unstable marker of long-term regular aspirin use for some patients who may only be temporarily using aspirin regularly. More objective and longitudinal sources of medication possession (eg, pharmacy claims) might help augment gaps in self-reported medication use. Despite the general advantages of EHR data in epidemiologic research, more subjective elements of the medical chart are often difficult to query, including direct physician advice to take aspirin, clinical judgments on some potential aspirin contraindications, and patients' primary intent of regular aspirin use (eg, CVD prevention, pain management). Future research would benefit from advancing methods to readily account for this information. Other limitations were the limited racial diversity of the source population relative to other parts of the country or more urban areas of the state.

This study is the first EHR-based examination of the pharmacoepidemiology of aspirin use for primary CVD prevention in the region. Several aspirin disparities were identified, which may help inform a profile of where and for whom future primary CVD care quality improvement initiatives (eg, academic detailing, clinical decision aids) could be optimally targeted. As EHRs become ubiquitous, primary CVD prevention surveillance methods outlined here could be further refined and adopted by other large health care systems, including those with geographically extensive service areas commonly found in Wisconsin and throughout the rural Midwest.[27] As part of the coming wave of American health care reforms, all health care systems will, in addition to providing high-quality care for sick patients, experience mounting expectations to monitor and improve the health of the entire populations they serve.

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CME

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Quiz: Identifying Opportunities to Improve Aspirin Utilization for the Primary Prevention of Cardiovascular Disease in a Regional Health Care System

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Appreciate the role of aspirin in the primary prevention of cardiovascular disease (CVD).
2. Understand patient factors associated with improved aspirin utilization in CVD prevention.
3. Improve their ability to council patients in whom aspirin is indicated for CVD prevention.

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QUESTIONS

1. Which of the following statements is false:
   - ❑ The primary prevention of CVD focuses on risk factor modification, including control of blood pressure and lipids and reducing platelet aggregation with low-dose aspirin.
   - ❑ Meta-analysis suggests that aspirin therapy lowers cardiovascular risk by about 15% over 7 years.
   - ❑ Current guidelines for aspirin therapy in primary prevention of CVD include all men over 40 years of age and all women over 50 years of age who do not have contraindications for aspirin.
   - ❑ The global risk equation from the Framingham Heart Study for estimating the 10-year risk of CVD includes information on age, gender, smoking, systolic blood pressure, total and high-density lipoprotein cholesterol, and diabetes.

2. Contraindications for aspirin use include intracranial bleeding, gastrointestinal bleeding, severe liver disease, and metabolic syndrome.
   - ❑ True
   - ❑ False

3. In the current study, the following characteristics were found to be significantly associated with higher aspirin use in those patients in whom aspirin therapy was indicated for primary CVD prevention:

   A. Older individuals
   B. Females
   C. Nonsmokers
   D. Lower body mass index (BMI)
   E. Diabetics

   - ❑ All of the above
   - ❑ A, B, and E only
   - ❑ A, C, and D only
   - ❑ B, C, and E only
   - ❑ A, C, and E only

4. A major conclusion of this study is that the most important motivating factor for regular aspirin use in patients for whom there is an indication for primary CVD prevention is a physician conversation.
   - ❑ True
   - ❑ False

• • •

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Osmotic Demyelination Syndrome

Narendranath Epperla, MD; Jillian Landeck; Salah Sabbagh, MD

ABSTRACT

Formerly known as central pontine myelinolysis, osmotic demyelination syndrome (ODS) is defined by a symmetrical destruction of myelin sheaths involving mainly the central portion of the basis pontis without evidence of vascular involvement. We report the case of a 60-year-old man who presented to the emergency department with a 2-week history of progressive confusion, memory loss, and lower extremity weakness with limited ambulation. A computed tomography scan of the head revealed areas of low attenuation within the pons, and brain magnetic resonance imaging (MRI) confirmed the changes as compatible with ODS.

CASE PRESENTATION

A 60-year-old man with a history of alcoholism and diabetes mellitus type 2 presented to the emergency department with a 2-week history of progressive confusion, memory loss, and lower extremity weakness with limited ambulation. He was unkempt in appearance and oriented to person and place with ataxia, grade 3 horizontal nystagmus, and dysmetria. Muscle strength was reduced symmetrically in both lower extremities. Blood tests were abnormal only for sodium at 120 mEq/L (range 133-144 mEq/L), while all other results, including ammonia level, were normal. Hyponatremia correction was accomplished according to current guidelines[1] over a period of 2 days (Figure 1). A computed tomography (CT) scan of the head revealed areas of low attenuation within the pons (Figure 2). Brain magnetic resonance imaging (MRI) confirmed the changes as compatible with osmotic demyelination syndrome (ODS) (Figure 3). He improved over the course of the next few weeks and was discharged to an alcohol and other drug abuse program for treatment of his alcoholism.

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DISCUSSION

Formerly known as central pontine myelinolysis, ODS is defined by a symmetrical destruction of myelin sheaths involving mainly the central portion of the basis pontis without evidence of vascular involvement.[2,3] The demyelination process usually occurs after rapid correction of chronic hyponatremia.[3-5] ODS is associated with conditions such as alcoholism, malnourishment, diabetes, hepatic failure, liver transplantation, cirrhosis, chronic renal failure, and malignancy.[6] The initial diagnosis is made clinically through behavioral disturbances and neurological deficits including confusion, mutism, dysarthria, dysphagia, bulbar and pseudobulbar paresis, hyperreflexia, paraplegia, quadriplegia, and seizures. In severe cases a locked-in state and coma may be seen. Cerebellar ataxia has been reported.[6-9]

This condition was thought to be uniformly fatal with only postmortem diagnosis, but after the introduction of brain imaging, asymptomatic and milder courses without neurological deficit have been reported.[10] Demyelination lesions occasionally can be detected by CT as low attenuation changes in the pons (Figure 1). The best noninvasive diagnostic technique is brain MRI, which facilitates better anatomical characterization. Typical MRI findings are of a homogeneous, well-defined region in the pons with symmetric hypodensity on T1-weighted images, hyperintensity on T2-weighted (Figure 3A), and Fluid Attenuation Inversion Recovery (FLAIR) images (Figure 3B), with no associated mass effect. In some cases the entire central pons is involved with only a thin rim of normal signal around it. These findings are not specific, and it is their anatomical distribution, combined with suggestive clinical features, that form the basis for the ODS diagnosis. MRI findings may lag behind clinical manifestations by as much as 4 weeks, so an initial negative result does not exclude ODS, and a repeat study in 2 weeks is recommended.[11,12] The extent of the lesions does not correlate with severity of the manifestations or final outcome; this must be remembered to

Figure 1. Rate of Serum Sodium Correction Over a 48-hour Period

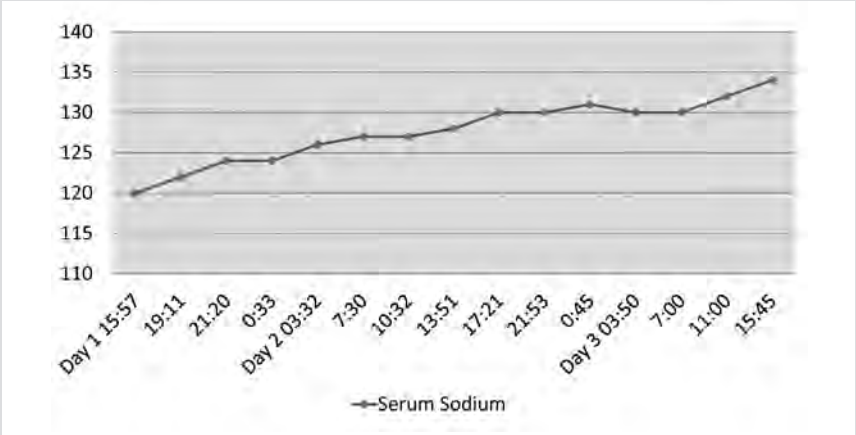


Figure 2. Unenhanced Computed Tomography (CT) Scan of the Head

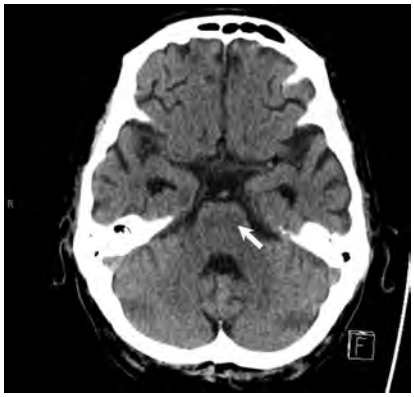
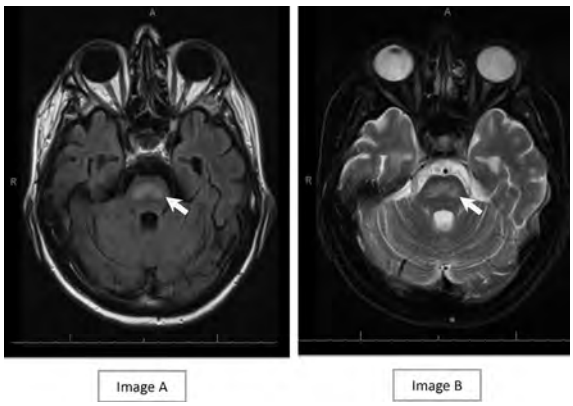


Image shows some patchy low density focus in the central pons (arrow).

Figure 3. Magnetic Resonance Images (MRI)



Fluid Attenuation Inversion Recovery (FLAIR) image (A) and T2-weighted magnetic resonance image (B) showing bilateral patchy high signal intensity within the pons (arrows). No mass effect is observed.

avoid a premature pessimistic prognosis based solely on severity of the radiographic abnormalities.[7,13,14]

CONCLUSION

The prognosis of ODS is heterogeneous, ranging from complete neurological recovery and resolution of MRI findings to progression of deficits and death. To date, there is no specific treatment available, so efforts to prevent its occurrence remain paramount. An appropriate rate of hyponatremia correction and treatment of comorbid conditions are essential to reduce the risk of suffering this potentially devastating disease.[7,8,15]

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Daptomycin-induced Acute Eosinophilic Pneumonia

Jayshil J. Patel, MD; Agith Antony, MD; Maria Herrera, MD; Randolph J. Lipchik, MD

ABSTRACT

Introduction: Daptomycin is a cyclic lipopeptide antibiotic with activity against gram-positive organisms. With increasing use, acute eosinophilic pneumonia is a rare, but potentially fatal adverse drug reaction that requires prompt recognition. The authors present a definite case of daptomycin-induced acute eosinophilic pneumonia.

Case Summary: A 61-year-old woman with poorly controlled type 2 diabetes who presented with bilateral foot pain was found to have bilateral calcaneal osteomyelitis. She was started on an antibiotic regimen that included daptomycin. Within 1 week, she developed fever, a dry cough, and shortness of breath and was treated for hospital-acquired pneumonia (HAP). Daptomycin was discontinued. Upon completion of therapy for HAP, the patient was subsequently restarted on daptomycin for continued therapy of bilateral calcaneal osteomyelitis. Within 48 hours of restarting daptomycin, the patient developed hypoxemic respiratory failure, bilateral pulmonary infiltrates, and peripheral eosinophilia. Bronchoscopic lavage revealed 30% eosinophils. Daptomycin-induced acute eosinophilic pneumonia was diagnosed. Daptomycin was discontinued, and the patient had complete resolution of symptoms, peripheral eosinophilia, and radiographic findings.

Discussion: Daptomycin initially was approved for skin and soft tissue infections, but its utility has expanded to bacteremia and endocarditis. Daptomycin-induced acute eosinophilic pneumonia is rare. A recent Federal Drug Administration review identified a total of 58 cases of daptomycin-induced acute eosinophilic pneumonia. Of these, 38 were possible, 13 were probable, and 7 were definite. We believe this is the 8th definite case of daptomycin-induced acute eosinophilic pneumonia to be reported in the literature.

INTRODUCTION

Drug-induced pulmonary eosinophilia is rare. The spectrum of disease ranges from a pulmonary infiltrate with eosinophilia, pleural disease, to acute eosinophilic pneumonia (AEP). AEP is a rare cause of acute respiratory failure, usually presenting with rapid onset of nonproductive cough and dyspnea with nonspecific radiographic findings.[1] The most common etiology is idiopathic.[1] There are reports of inhalational exposures and drug-induced AEP.[1] Recently, the Food and Drug Administration (FDA) reported 58 cases of daptomycin-induced AEP, 7 of which were definite.[2] Here, we present the 8th definite case of daptomycin-induced acute eosinophilic pneumonia.

CASE PRESENTATION

A 61-year-old woman with poorly controlled type 2 diabetes, complicated by nephropathy and neuropathy, presented to the emergency department with bilateral foot pain for 1 week. She reported draining heel ulcers with central eschars that were increasing in size. There were no fevers or chills. Vitals signs were normal. The physical exam was pertinent for bilateral lower extremity swelling, erythema, and warmth. The right heel had a 5 cm x 6 cm ulcer with insensate eschar at the base and purulent drainage from the borders. The left heel had a 2 cm x 3 cm ulcer with similar characteristics. Magnetic Resonance Imaging (MRI) revealed bilateral calcaneal osteomyelitis with left tibial and fibular fractures. Due to multiple drug allergies, the patient was started on daptomycin, aztreonam, and metronidazole to complete 6 weeks of therapy.

On day 7 of therapy, the patient developed shortness of breath and a dry cough. Vitals signs were normal except for oxygen saturation of 90% on 3 L/min. Exam revealed inspiratory crackles throughout both lungs with decreased breath sounds. Chest radiograph (CXR) showed new bilateral pulmonary infiltrates (Figure 1). White blood cell count was 16,100 per μL (reference range 4000-11,000 per μL) with 15% eosinophils (reference range 0 to 6%). She was thought to have hospital-acquired pneumonia (HAP). Due to unsuitability of daptomycin for pneumonia, it was changed to linezolid. Aztreonam and metronidazole were continued. Symptoms and peripheral eosinophilia resolved, and all cultures were negative.

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Figure 1. Portable Anterior-posterior (AP) Chest Radiograph Demonstrating Diffuse Bilateral Alveolar Infiltrates with Bilateral Pleural Effusions.

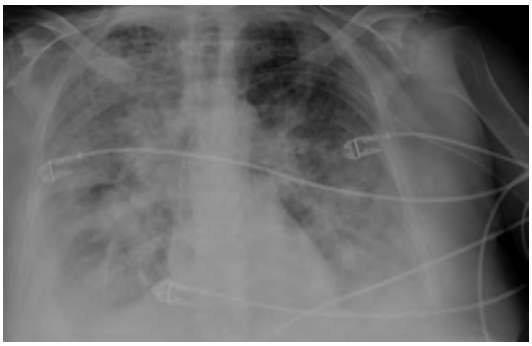
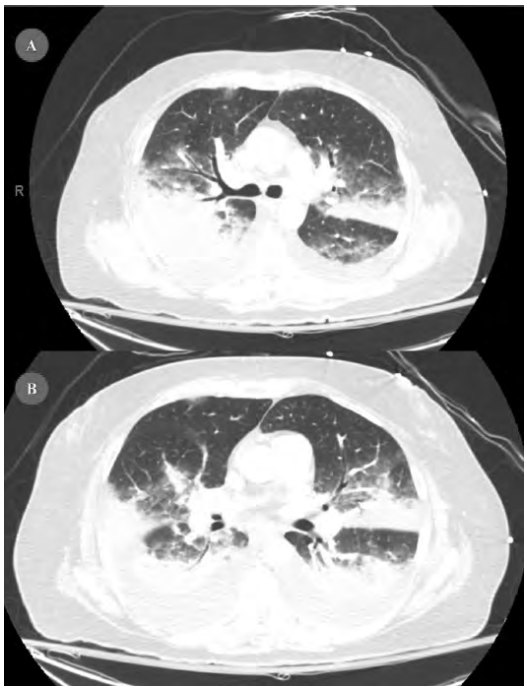
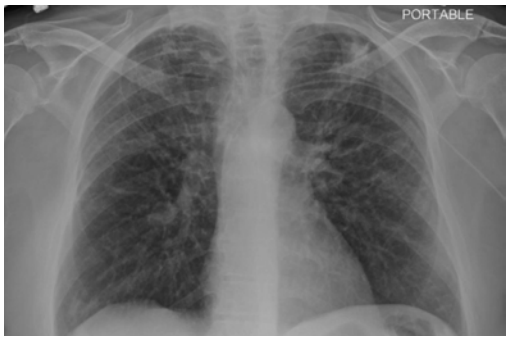


Figure 2. Chest Tomography Demonstrates Dense Bilateral Airspace Opacities in Both (A) Upper and (B) Lower Lung Fields.



Upon completion of 8 days of therapy for HAP, daptomycin was resumed for the osteomyelitis. Within 2 days of restarting daptomycin, the patient was admitted to the intensive care unit for hypoxemic respiratory failure requiring intubation. White blood cell count was 21,200 per μL with 11.3% eosinophils. Chest computed tomography (CT) showed bilateral pleural effusions and diffuse bilateral patchy infiltrates (Figure 2). Bronchoalveolar lavage (BAL) demonstrated 30% eosinophils. The Naranjo algorithm is a questionnaire used to determine whether an adverse drug reaction (ADR) is actually due to the drug and not other factors.[3] A diagnosis of daptomycin-induced acute eosinophilic pneumonia was made based on a Naranjo score of 9, indicating a definite ADR. Daptomycin was discontinued and corticosteroids were started to hasten recovery. Within 72 hours, the patient was extubated with complete clinical resolution of symptoms. Infectious workup was negative. There was resolution of peripheral eosinophilia and CXR demonstrated marked improvement (Figure 3).

Figure 3. Portable Anterior-posterior (AP) Chest Radiograph Demonstrates Resolution of Dense Bilateral Opacities.



DISCUSSION

Pulmonary eosinophilia is a heterogeneous group of disorders that share the common finding of an increased number of eosinophils in the lung parenchyma.[4] These entities include helminth infections, Churg-Strauss syndrome, allergic bronchopulmonary Aspergillosis (ABPA), acute and chronic eosinophilic pneumonias, and reactions to medications and toxins.[1] Drug-induced pulmonary eosinophilia can present as an asymptomatic infiltrate, a pleural effusion, and/or AEP.[5] AEP commonly presents with an acute onset of fever, dry cough, and shortness of breath that can progress to hypoxemic respiratory failure.[6] Corresponding radiographic findings may include new infiltrates, but changes are nonspecific.[6] AEP is idiopathic in the majority of cases.[6] Medications reported to induce AEP include nonsteroidal anti-inflammatory drugs (NSAID), antidepressants, antipsychotics, and antimicrobials such as nitrofurantoin, minocycline, and daptomycin.[5] Diagnosis of AEP is based on greater than 25% eosinophils in lung tissue or BAL fluid in the setting of pulmonary infiltrates, thus obtaining a BAL remains an important intervention.[6]

Solomon and Schwartz[5] described 5 criteria that could be used to confidently diagnose drug-induced AEP: (1) presence of AEP, as defined by the aforementioned criteria, (2) presence of a causative drug with appropriate temporal relationship, (3) no other cause of AEP such as a fungal or parasitic infection, (4) clinical improvement after cessation of the drug, and (5) recurrence of AEP with rechallenge to the drug. When the etiology is uncertain, lung biopsy should be performed. Histopathology demonstrates acute and organizing diffuse alveolar damage with eosinophil and other inflammatory cell infiltration within lung parenchyma.[6]

Table. Definite Cases of Daptomycin-induced Acute Eosinophilic Pneumonia (AEP) that Underwent Drug Rechallenge

Age and Gender	Indication	Reaction	BAL eosinophil (%)	Outcome
61-year-old woman[a]	Bilateral calcaneal osteomyelitis	Dyspnea, dry cough, and respiratory failure, with recurrence within 2 days of rechallenge requiring mechanical ventilatory support.	30	Daptomycin held, corticosteroids started, and patient extubated within 3 days with full recovery.
60-year-old man[4]	MSSA[b] endocarditis	Fever, dyspnea, and respiratory failure requiring mechanical ventilation, with recurrence within 4 hours of rechallenge.	26	Daptomycin held, corticosteroids started, and patient extubated within 3 days with full recovery.
60-year-old man[8]	Left foot osteomyelitis	Fever and dyspnea with increased oxygen requirements, with recurrence within 2 days of rechallenge.	81	Daptomycin held, no mention of corticosteroids, reported "prompt" recovery.

[a] Our case
[b] Methicillin-sensitive *Staphylococcus aureus*
Abbreviation = BAL, Bronchoalveolar lavage

Daptomycin is a cyclic lipopeptide antibiotic with activity against gram positive organisms. In the lung, daptomycin irreversibly binds to surfactant, rendering the daptomycin inactive with sequestration of the drug.[7] Thus, daptomycin is unsuitable for treatment of pneumonia.[7] Daptomycin-induced AEP is rare. A recent review by the FDA revealed 7 definite, 13 probable, and 38 possible cases of daptomycin-induced AEP.[2] In this review, definite cases were characterized by concurrent exposure to daptomycin, fever, dyspnea with increased oxygen requirement, new pulmonary infiltrates, bronchoalveolar lavage with >25% eosinophils, and clinical improvement after withdrawal of daptomycin.[2] Among the 7 definite cases, the onset of symptoms ranged from 10 to 28 days after initiation of daptomycin therapy. Of the 7 definite cases, 2 reported recurrence of AEP on rechallenge with daptomycin.[2] Table 1 compares these rechallenge cases with our patient. Recurrence of symptoms was seen anywhere from 4 hours to 2 days from rechallenge. These patients again demonstrated clinical recovery after repeat withdrawal of daptomycin. In addition to drug cessation, 5 of the 7 definite cases also were given systemic steroids.

The mechanism of daptomycin-induced AEP remains unclear. A proposed hypothesis is that the drug's sequestration in the lung as an inactive drug could lead to it acting as an antigen, being taken up by alveolar macrophages, and culminating in an inflammatory response.[4] As with other eosinophilic disorders, the eosinophil is under the control of the lymphocyte.[6] Thus, alveolar macrophages recruit T helper-2 cells (Th-2), which in turn release interleukin-5 (IL-5).[2] The accompanying eosinophil granules released into the interstitium and into alveoli can inflict considerable damage to the lung.[6]

Daptomycin initially was approved for treatment of complicated skin and soft tissue infections, but its use continues to expand for bacteremia and endocarditis.[2] Clinicians must be aware of its potential to cause AEP, especially since the entity has a rapid onset with poor morbidity. A drug-induced etiology of AEP should be suspected if the patient has a temporal exposure to the offending drug with corresponding signs and symptoms with findings of greater than 25% eosinophils on BAL. Importantly, infectious etiologies should be ruled out, and if the diagnosis is uncertain, lung biopsy may be necessary. The management of daptomycin-induced AEP necessitates discontinuation of the drug. A brief course of corticosteroids can hasten recovery. Given the morbidity of the reaction, rechallenge is not recommended. Our case underscores the importance of not rechallenging a patient with daptomycin-induced AEP. Our case adds to the literature the 8th definite case of daptomycin-induced AEP. In the other 2 definite cases where a rechallenge was done, a Naranjo causality score was not mentioned.[4,8] Based on our patient's Naranjo causality score of 9 and fulfillment of all Solomon and Schwartz[5] criteria, ours is the 3rd definite case of daptomycin-induced AEP with rechallenge.

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Streptococcus Infection in a Newborn

Jessica Molinaro, BA; Gary Cohen, MD; Kris Saudek, MD

ABSTRACT

Streptococcus salivarius is an uncommon cause of infection in neonates. Normally present in the oral flora of humans, *S salivarius* is the least pathogenic member of the viridans group streptococci and is often considered a contaminant when detected on blood culture. While rare, it has been shown in the literature to cause clinically relevant bacteremia and other invasive infections typically in the immunocompromised. We report the case of a well-appearing 1-day-old female with sequential positive blood cultures for *S salivarius.* This case has important implications as it demonstrates that *S salivarius* should not be automatically ruled out as a contaminant when isolated on blood culture.

INTRODUCTION

Neonatal bacterial infections can be life-threatening, making proper diagnosis and timely treatment of these infections essential. Most bacterial infections are contracted during or immediately after birth and bacteremia/septicemia has been found to be one of the leading causes of morbidity and mortality in infants.[1] Neonates' immunoimmaturity increases their risk for acquiring serious bacterial infections. Common sources of neonatal bacterial infections include Group B streptococcus (GBS), *E coli, Listeria* and *Staphylococcus aureus.* Numerous reports have shown the ability of these bacteria to cause bacteremia, septicemia, and meningitis.

There are several less commonly known sources of neonatal bacterial infection that also have been reported. The viridans group streptococci (VGS) represent a group of bacteria that colonize humans most notably in the oral cavity, although some species inhabit very discrete niches. While *S salivarius* shows a predilection for the dorsum of the tongue, its close relative *Streptococcus bovis* inhabits the gut.[2] Clinically, the organisms behave similiarly.[3] While bacteria of this group generally are considered to be of low virulence, studies have shown they can cause life-threatening disease in neonates, children, and adults.[4,5]

As the virdans streptococci colonize the human oral cavity immediately after birth, they are commonly considered a contaminant when isolated on blood culture. While isolation is infrequent, reported at 2.6% of positive blood cultures, they should not automatically be considered a contaminant.[5] As many as 32% of isolates have indicated clinically relevant bacteremia.[6] Moreover, with isolation of a single organism of the virdans streptococci (such as *S salivarius*) or when a repeat blood culture is positive for a single organism, the significance of isolation increases. In the following description, *S salivarius* was isolated on 2 serial blood cultures, increasing the suspicion that this was not a contaminant but a clinically significant finding.

CASE HISTORY

The patient was a full-term, white female newborn delivered to a 19-year-old gravida 2, para 1 (now 2) single, unemployed mother at 40 2/7 weeks gestation via normal spontaneous vaginal delivery after an uncomplicated pregnancy. The infant had Apgar scores of 8 and 9 at 1 and 5 minutes respectively and birthweight of 3180 grams.

Maternal lab results were significant for being GBS positive. She received 2 doses of intrapartum clindamycin. Despite the infant being clinically well and afebrile at admission to the newborn nursery, a complete blood cell count (CBC) with manual differential and blood culture were obtained; maternal intrapartum antibiotic prophylaxis with clindamycin and the lack of sensitivity data on her isolate was considered inadequate by GBS guidelines at that time.[7] While the initial CBC was normal (white blood cell = 16.7, hemoglobin = 17.4, hematocrit = 52, platelets = 327, band cells = 3%, segmented neutrophils = 63%, lymphocytes = 24%, monocytes = 9%) the blood culture showed gram positive cocci in chains. Lumbar puncture (LP) was performed and found to be normal. The blood culture later identi-

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fied the gram-positive species as *S salivarius,* and a repeat blood culture confirmed this finding. A chest x-ray also was performed and interpreted as negative for pathology.

Our initial examination was unremarkable. The infant was well appearing, demonstrating no signs or symptoms of infection and was feeding well. She was afebrile and all vital signs were stable and normal. Physical examination of all systems was normal. The patient was treated for 10 days on intravenous penicillin. An echocardiogram was performed due to risk of endocarditis with this particular species. The patient was monitored on the unit for the 10-day course of IV antibiotics. Throughout this course, the patient demonstrated no signs or symptoms of infection. The repeat blood culture after the antibiotic regimen was started was negative, and the LP culture was also negative. The echocardiogram was negative for endocarditis. The patient fed well and gained weight and had a discharge weight that surpassed birth weight. The patient's condition on discharge was excellent.

DISCUSSION

Streptococcus salivarius is a relatively rare cause of invasive infections in neonates and is commonly considered a contaminant when isolated as it is part of the human oral flora.[6] When it has been recognized as a cause of life-threatening infection such as infective endocarditis and septicemia, it is most commonly in the context of a patient who is immunocompromised.[3]

There are reports in the literature that show infection can occur in the context of immunocompetent individuals. Ferrier et al examined the features of infective endocarditis (IE) in childhood. While most cases of IE occur in the setting of structural heart disease or congenital heart defect, the authors report that 8% to 10% of cases of IE were in structurally normal hearts. The bacteria causing these infections were most commonly the viridans streptococci and *Staphylococcus aureus*.[8]

Cheung et al reported a case of a 4-week-old neonate with late-onset *S bovis* meningitis. *S bovis* is an uncommon cause of neonatal meningitis. When it does cause neonatal infection, it is often in the context of an individual with prior gastrointestinal disease or possible immunosuppression. The neonate in their case report was previously healthy.[9] Gavin et al reported a case of *S bovis* sepsis in a 3-day-old neonate. The infant had no predisposing medical conditions.[10] Like *S bovis, S salivariu*s is an uncommon cause of invasive disease in neonates. Most reports in the literature have shown it to cause serious infection in the setting of immunocompromised hosts. Ruoff et al reported 6 cases of sepsis due to *S salivarius* in children with underlying malignant disease.[11]

Here we report a case of neonatal *S salivarius* bacteremia in an infant with no significant medical disease. And while the bacteremia in our case was not picked up because the infant was symptomatic, it is entirely possible that the infant would have decompensated without early identification and treatment. The worst case scenario would have been one in which this neonate was discharged after 2 days with her mother and then developed sepsis, meningitis, or endocarditis at home. The infant's risk was heightened given the young age of the mother and limited financial resources and support. This is especially important as *S salivarius* is commonly considered a contaminant on isolation and ignored. These findings have direct implications for the rapid identification, proper treatment, and optimal care of neonatal infections.

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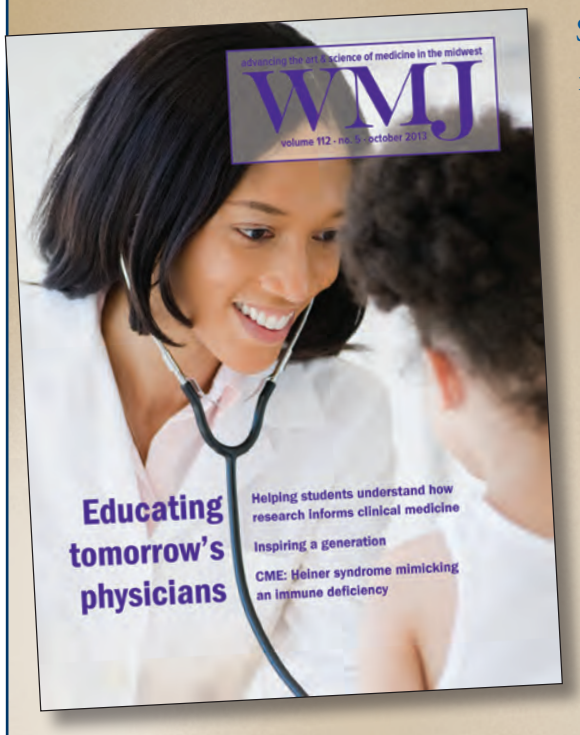

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MetaStar Shows Marked Improvements for Medicare Patients, Looks to Future

Jay A. Gold, MD, JD, MPH

For decades under the federal Quality Improvement Organization (QIO) program, QIOs under contract with the Centers for Medicare & Medicaid Services (CMS) have worked with Medicare physicians, providers, beneficiaries, and others to improve the quality of their care. This is a year of transition for the program, which has served as the country's longest-standing nationwide program to improve patient care, improve the health of the population, and reduce or control health care cost. MetaStar has served as the QIO for Wisconsin since the program's inception.

During the most recent QIO contract (August 2011-July 2014), MetaStar can point to a number of noteworthy improvements in Wisconsin:

- Hospital admissions declined by 15% and 30-day hospital readmissions declined by 19%.
- Hospitals participating with MetaStar saw a 22% reduction in catheter-associated urinary tract infections (CAUTI), a 6% reduction in the utilization of catheters, and a more than 31% reduction in incidence of *Clostridium difficile* infections.
- 193 nursing homes participated in the MetaStar-led Wisconsin Quality Coalition, a statewide collaborative effort to improve resident care.
- Urinary tract infections (UTI) in nursing homes declined by 14%. This means that approximately 53 UTIs were prevented every month. The average cost to treat a UTI is $896 in a nursing home. Given the UTIs prevented and the average cost of treating a UTI, the 193 nursing homes in the Wisconsin Quality Coalition are saving approximately $47,488 every month.

The quality improvements in our state are also reflected in figures across the country. According to data released by CMS, national gains include:

- 95,000 hospitalizations and 27,000 hospital readmissions among Medicare beneficiaries have been prevented.
- 85,149 fewer days were spent with urinary catheters for Medicare beneficiaries.
- 5021 nursing homes participated in a collaborative effort.
- 3374 pressure ulcers were prevented or healed in 787 nursing homes.
- 44,640 potential adverse drug events were prevented.
- 1826 health care professionals were assisted with Physician Quality Reporting System (PQRS) electronic health record (EHR) 2012 reporting—impacting millions of Medicare beneficiaries.

Looking Forward

The new CMS contract cycle for Medicare quality improvement began on August 1, 2014, and will continue for the next 5 years. CMS restructured its contracts so that different organizations now handle some of the tasks once accomplished by a single state-based QIO. KEPRO, an Ohio-based organization, now processes Medicare quality of care case reviews, discharge/discontinuation of service, and other related review services for Wisconsin beneficiaries. Florida Medical Quality Assurance, Inc. (FMQAI) is providing technical support to hospitals participating in inpatient and outpatient quality reporting.

Under a new Quality Innovation Network structure, MetaStar has teamed with organizations in Minnesota (Stratis Health) and Michigan (MPRO) to attain the new Medicare quality improvement goals. The 3 organizations are working together to facilitate improvement throughout the region.

The priorities for CMS in the next 5 years include:

- **Healthy People, Healthy Communities:** prevention and treatment of chronic disease, including reducing disparities in diabetes care and improving cardiac health.
- **Better Health Care for Communities:** patient safety issues such as improved care coordination and reduction of health care-associated infections in hospitals and health care-acquired conditions in nursing homes.
- **Better Care at Lower Cost:** through value-based programs.
- **Other Technical Assistance and Special Innovation Projects:** broad categories for emerging issues.

MetaStar welcomes participation by all who wish to contribute to better care, better health, and lower costs through improvement. Many of our projects will be recruiting physicians and organizations to join in the next 6 months, and, as always, our assistance and educational resources are provided at no cost for participants. For more information, visit www.metastar.com, or contact MetaStar's Chief Medical Officer, Jay A. Gold, MD, JD, MPH, at 608.274.1940.

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Dr Gold is senior vice president and chief medical officer for MetaStar. This material was prepared by the Lake Superior Quality Innovation Network, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the US Department of Health and Human Services. The materials do not necessarily reflect CMS policy. 11SOW-MI/MN/WI-A1-14-02 082614

Ask This One Question

W. Stancil Starnes, JD

Editor's note: The Wisconsin Medical Society helped form PIC WISCONSIN in 1985 to ensure the availability of medical professional liability insurance for Wisconsin physicians. Today the Society continues to endorse ProAssurance (formerly PIC WISCONSIN) to provide professional liability insurance coverage for physicians.

"What have you done for me lately?" That's certainly one of the most common questions asked in our society today, and it's one I would encourage you to ask of your professional liability insurer.

When you ask that question of ProAssurance, we're proud of the answers we can provide you. Our long-term commitment that began with PIC Wisconsin in 1985 has been enhanced since PIC joined ProAssurance. It's certainly a commitment no other professional liability carrier can match.

Most recently, ProAssurance worked in partnership with the Wisconsin Medical Society Holdings Corporation to develop the Wisconsin Medical Society Holdings Risk Purchasing Group, LLC (WMSH RPG). This innovative medical liability insurance program offers customized protection and special pricing to physicians practicing in multispecialty groups of 50 or more—the kind of medical groups that have been common in Wisconsin for years, making Wisconsin physicians leaders in the evolving world of American health care. The WMSH RPG program is available to qualified groups wherein all physicians agree to:

- participate in integrated clinical risk management programs developed by the WMSH RPG.
- be a part of state quality and efficiency measurements that are enhancing patient safety and improving clinical outcomes.

For those physicians who do not participate in the WMSH RPG, our commitment is equally solid. Among the benefits and special coverages available to Wisconsin Medical Society members are meaningful discounts for membership, attendance at approved risk management seminars, and installation and effective use of an approved electronic medical record system.

ProAssurance also recognizes and rewards the practice of good medicine with loss-free credits. In addition, ProAssurance's Wisconsin physician insureds have an extra $1 million of Contingent Liability coverage should the Injured Patients and Families Compensation Fund deny coverage for a judgment above $1 million. Our policy features have evolved in anticipation of new risks. For example, we offer:

- separate limits of liability for the contractual liability of insured practices.
- coverage for physicians also serving as medical directors for qualified facilities.
- coverage for defense costs when responding to certain governmental investigations, such as those dealing with Medicare billing errors and omissions and disciplinary proceedings or hearings.

Today's data-centric culture places great demands on the security of health care records. ProAssurance helps physicians manage this risk as well—providing insureds with defined CyberAssurance coverage, including limited reimbursement for data recovery costs.

Working with the Wisconsin Medical Society, ProAssurance provided pivotal support to the effort to bring greater fairness to laws regarding informed consent in the state. Under this new law, Wisconsin physicians may rely on their clinical judgment when informing patients about potential tests and treatments that are most appropriate for their conditions. The impetus for this change was a multimillion dollar verdict under the old law, which required physicians to explain tests and treatments that were not likely to benefit their patients.

In addition to our unparalleled commitment to work with organized medicine for the benefit of all Wisconsin physicians, ProAssurance's commitment to Wisconsin insureds is clear. Our grassroots-level outreach is unrivaled in the state.

ProAssurance Regional Advisory Boards (RABs) bring together physician leaders so that

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Stan Starnes is chairman and chief executive officer of ProAssurance Corporation, the parent company of ProAssurance Casualty Company (formerly PIC Wisconsin), the endorsed medical professional liability carrier of the Wisconsin Medical Society.

we can listen and learn from them. In Wisconsin more than 30 physician leaders from around the state meet 4 times a year to engage in meaningful dialogue about the state of health care, emerging medical liability trends, and how best to deal with difficult claims and medical issues. Through this process, ProAssurance stays ahead of the curve in assisting physicians practicing in Wisconsin and surrounding states.

Our Claims and Underwriting Committees (CUCs) provide a direct voice for the physicians we insure. In Wisconsin, a group of 14 experienced physicians and health care leaders—leaders in their specialty and community—meet to assist us in reviewing the toughest claims and working through challenging underwriting decisions. They ensure that ProAssurance remains plugged into the fabric of Wisconsin medicine.

If you would like to know more about our Wisconsin RABs and CUCs, call 800.282.6242 and ask for Richard Walter, claims vice-president, or Tom Lownik, underwriting vice-president, located in our Madison office. They welcome your interest and will discuss opportunities for you to become involved as openings occur.

The medical liability environment in Wisconsin remains stable thanks to (1) the involvement of active, concerned physicians who lend their advice and counsel, (2) ProAssurance's willingness to provide the finest lawyers and an unfettered defense of your claim, and (3) the efforts of the Wisconsin Medical Society.

We pledge to each of our insured physicians that ProAssurance's commitment in the future will match the unsurpassed advocacy we've demonstrated in the past. Our financial strength ensures we have the resources to make that promise. Our dedication to the principles of *Treated Fairly* demonstrates our commitment. You see, it's not only about what we have done lately; it's about what we will do, and how we will do it in the future.

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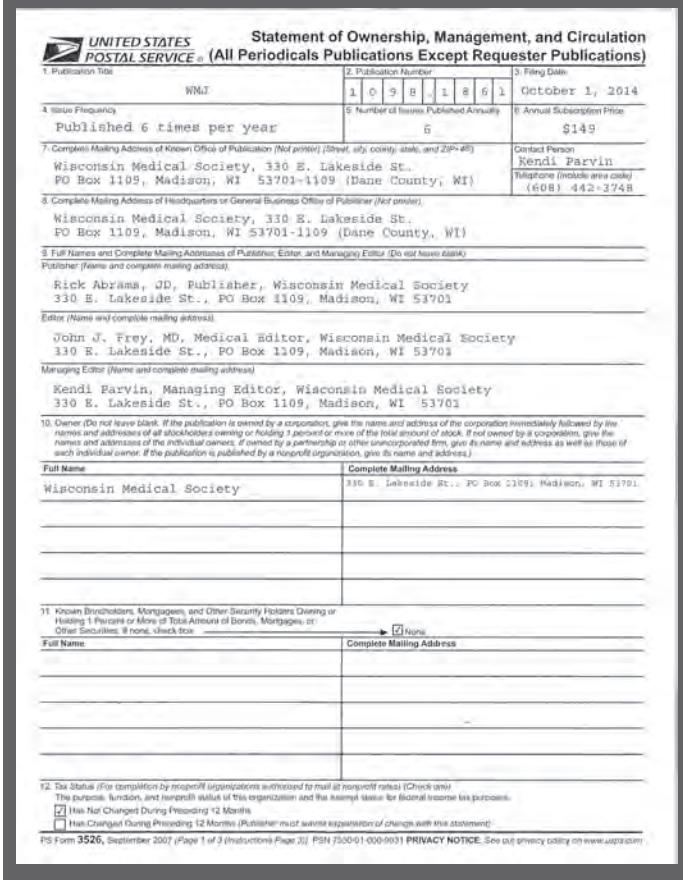

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Katherine Sanders has a BS, MS and PhD in Industrial & Systems Engineering from UW-Madison. She specializes in human factors and sociotechnical systems engineering, essentially the health and productivity of people at work. Her academic work as an occupational stress researcher gave rise to a commitment to design programs to support professionals in high burnout occupations. She's one of a small number of PhD systems engineers focused on occupational health, and has a specific interest in the well-being of healers.

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