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# Geodemographic Features of Human Blastomycosis in Eastern Wisconsin

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<b>Purpose</b>	Blastomycosis is an endemic fungal infection. In rural northern Wisconsin, blastomycosis cases are associated with certain environmental features including close proximity to waterways. Other studies have associated blastomycosis with particular soil chemicals. However, blastomycosis also occurs in urban and suburban regions. We explored the geodemographic associations of blastomycosis cases in the more urban/suburban landscape of eastern Wisconsin.
<b>Methods</b>	We conducted a retrospective study of 193 laboratory-identified blastomycosis cases in a single eastern Wisconsin health system, 2007–2015. Controls were 250 randomly selected cases of community-diagnosed pneumonia from a similar time period. Geographic features of home addresses were explored using Google Maps. Categorical variables were analyzed with chi-square or Fisher's exact tests and continuous variables by two-sample t-tests. Stepwise regression followed by binary logistic regression was used for multivariable analysis.
<b>Results</b>	Compared to pneumonia cases, blastomycosis cases were younger (47.7 vs. 55.3 years) and more likely to be male (67.9% vs. 45.6%), nonwhite (23.2% vs. 9.7%) and machinists, automobile workers/mechanics or construction workers (32.7% vs. 7.2%); $P < 0.001$ for all. These relationships remained significant on multivariable modeling. Case home sites, compared to controls, were more likely to have water frontage, (17.6% vs. 7.5%, $P = 0.004$ ), be $> 0.5$ acres (30.4% vs. 14.2%, $P = 0.0002$ ), be $< 0.25$ miles from an automobile repair facility or junkyard (35.9% vs. 19.4%, $P = 0.0005$ ), and be $< 0.1$ miles from a park, forest or farm field (54.9% vs. 39.6%, $P = 0.002$ ). Only the latter association remained on multivariable analysis.
<b>Conclusions</b>	Eastern Wisconsin blastomycosis case subjects were younger, more often male and more likely to live near parks/forests/fields. Novel associations of blastomycosis cases with machinery- and automobile-related occupations and/or facilities should be further explored. ( <i>J Patient Cent Res Rev.</i> 2016;3:90-98.)
<b>Keywords</b>	<i>Blastomyces dermatitidis</i> ; fungal ecology; mycoses; environmental exposure; blastomycosis

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Blastomycosis is a potentially serious systemic and cutaneous fungal infection endemic to eastern North America (and parts of India and Africa).<sup>1</sup> Disease is acquired from the environment by inhalation of spores of the etiologic fungi *Blastomyces dermatitidis* or *Blastomyces gilchristii*.<sup>2</sup> Blastomycosis incidence rates are particularly high in Wisconsin compared to

the rest of the nation.<sup>3</sup> While reports are emerging from lesser endemic portions of the state,<sup>4,5</sup> most epidemiologic investigations of sporadic and outbreak cases have focused on rural northern and central Wisconsin.<sup>6-17</sup> Despite generally lower incidence rates of blastomycosis in more urban eastern and southeastern Wisconsin counties, case numbers often meet or exceed those from their rural Wisconsin counterparts. For example, recent annual incidence rates for rural Vilas County, Wisconsin (27/100,000)<sup>10</sup> equate to 5.5 cases per year from this county. Whereas a conservative estimate of blastomycosis rate in

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Milwaukee County (1/100,000)<sup>5</sup> equates to 9.5 cases per year, and compares well to average endemic area rates in the United States (approximately 1–2 cases per 100,000 people per year).<sup>18</sup>

The precise ecologic niche of *Blastomyces* species remains incompletely defined. Compared to other soil bacteria and fungi, these fungal species are poorly competitive in the environment; however, their ability to survive harsh conditions and rapid environmental change may enable them to survive and even thrive for certain periods of time.<sup>9,11,19–22</sup> *Blastomyces* fungi tolerate a wide range of temperatures and periods of relative drought.<sup>19,20</sup> Antecedent weather conditions appear to partially predict subsequent blastomycosis cases in at least certain regions.<sup>9–11,23</sup> In addition, soil levels of certain chemicals such as ammonia,<sup>21</sup> copper and mercury<sup>3</sup> may be important to the microecology of *Blastomyces*.

As summarized elsewhere in this issue<sup>24</sup> — although some have demurred<sup>25,26</sup> — there appears to be good circumstantial evidence that blastomycosis can be acquired on one's home property.<sup>27–31</sup> For these reasons, we used home addresses of blastomycosis cases to explore environmental associations of this disease in our previous Wisconsin studies. In one such study, home addresses were compared to certain geographic features utilizing a geographic information system.<sup>12</sup> In other studies the home sites were personally visited, however, observations of some portions of properties and the ability to very accurately measure distances to the nearest feature of interest were limited by observation from the nearest public access.<sup>5,13–16</sup> Another recent study of blastomycosis endemic regions nationwide used only county level variables.<sup>3</sup> Thus, important geographic features or sources of chemical exposure on or in close proximity to the home sites of blastomycosis cases could have escaped observation.

The aim of this study was to explore geodemographic associations among home properties of blastomycosis cases in predominantly urban and suburban eastern Wisconsin, utilizing a group of community-diagnosed pneumonia cases as controls.

## METHODS

### Setting

Data for this study was drawn from a large, integrated health system that includes 15 hospitals and 159

outpatient clinics throughout eastern Wisconsin and extreme northeastern Illinois. Geologically, eastern Wisconsin consists of glacial lowlands and plains, interspersed with ridges and other glacial surface features. The predominant bedrock is limestone.<sup>32</sup> The majority of the region is farmland, with an increasing minority of forest cover.<sup>33</sup> The area contains the majority of the state's urban and suburban population. The largest county, Milwaukee County, is located in southeastern Wisconsin and has a 2014 U.S. Census population estimate of 956,406.

### Subject Selection

For this retrospective review of electronic medical records, blastomycosis cases from July 2007 to July 2015 (N=193) were obtained from a comprehensive database of laboratory-diagnosed individuals with blastomycosis housed at our institution's affiliated laboratory.

Control subjects were obtained from a previously assembled cohort of 250 randomly selected adult patients with community-acquired pneumonia (CAP) diagnosed by primary care clinicians in an outpatient facility from October 2006 to July 2013. Patients were identified by ICD-9 diagnostic codes 480–486 (and subsets) with the following diagnoses excluded from the study: cancer, bronchiectasis, blood disorders, tuberculosis, HIV/AIDS, tracheostomy/ventilator dependence and pregnancy. Details of this cohort are described in detail elsewhere in this issue.<sup>34</sup>

All activities were reviewed and approved by the local institutional review board.

### Data Sources

Case and control subjects were reviewed in the electronic medical records. Basic demographic data were collected, including age, gender, race/ethnicity, occupation and street address. When multiple street addresses or occupations were available, every attempt was made to use the one most closely associated with the occurrence of the index illness. Google Maps' map view and satellite imagery ("Earth View") were used to explore the case or control home site and nearby environments (Google Maps/Google Earth Imagery, 2015). We chose a novel approach of utilizing Google Maps for viewing and measurement of nearby features, thereby avoiding the difficulties in observation

**Table 1.** Descriptions of racial/ethnic, occupational and surface geographical and geological variables used in univariable analysis of blastomycosis cases in eastern Wisconsin

Variable	Definition/Description	Categorical unit(s)
Race/ethnicity	Self-identification in electronic medical record	White Black Native American Asian/Pacific Islander Other Hispanic/Latino Two or more
Occupation	Self-identification in electronic medical record or public description of place of business listed under “occupation”	Machinist/autoworker or repair/ construction Trucker/postal delivery Machinery/auto-related such as mechanical engineer or auto sales Teacher Other – various
Water distance	Linear distance calculated from home site to nearest body of water (see below)	None within 1.5 mi ≤ 0.10 mi 0.10 mi < distance ≤ 0.25 mi 0.25 mi < distance ≤ 0.50 mi 0.50 mi < distance ≤ 1.0 mi > 1.0 mi
Park distance	Linear distance calculated from home site to edge of nearest park boundary designated on Google Maps (empty lots not included)	
Auto business distance	Linear distance calculated from home site to nearest auto-related business (see below)	
School distance	Linear distance calculated from home site to edge of nearest elementary, middle, high school or college property	
Worship distance	Linear distance calculated from home site to edge of nearest church, temple, synagogue, mosque or other community center for religious faith property	
Water type	Lakes and rivers only coded when specific body of water suggested such (ex: Lake Michigan, Fox River); otherwise coded as ponds and streams, respectively  No wetlands were designated by Google, therefore none were coded	None within 1.5 mi Lake River Stream/creek Wetland Pond
Water frontage	Visually obvious property border abuts body of water (incl. small ponds engulfed by property)	Present Absent
Park type*	Parks with few, if any, trees and/or a distinguishable playing field (baseball, soccer, etc.) coded as “1”  Parks with trees (of any type) coded as “2” unless trees so thick as to block bird’s eye view of grass, in which case coded as forest  Parks with any water frontage/engulfed water feature (as physically seen in Earth View or as designated by light blue in “map” view) coded as “3”	None within 1.5 mi Grass/baseball/school Trees and grass Park with pond/stream/other water Other
Auto business type	Designated according to Google summary of type of auto-related business	Codes included: “auto repair,” “car repair,” “auto body,” “mechanic,” “used car dealer,” “car dealer,” “salvage,” “junkyard,” “car wash” Other auto-related businesses
Street type	Street/road/highway designated in subject street address	Dirt/unpaved Cul-de-sac Neighborhood street Busy street/boulevard County/state highway U.S. interstate highway

**Table 1 (cont).** Descriptions of racial/ethnic, occupational and surface geographical and geological variables used in univariable analysis of blastomycosis cases in eastern Wisconsin

Variable	Definition/Description	Categorical unit(s)
Neighborhood type	Determined by 2010 U.S. Census maps (lines and colorings denoted in right column refer to these maps)	Urban — within green lines and colored areas (no patterning) Suburban — within colored areas (outside green lines) or within green lines and outside colored areas (patterning) Rural — within township but outside colored areas and green lines Farm — without all boundaries
House type	Assumed “house” unless shown otherwise by: address indicating apartment/lot number; residence within mobile home community area; two sets of street numbers/doorbells indicative of a duplex living arrangement	House Mobile home Apartment Duplex
Property size	Rough rectangular measurements of property boundaries obtained, then converted into acreage	< 0.5 acres < 2.0 acres > 2.0 acres
Yard type	Designated by type of yard that covers majority of the property	Grass Grass and deciduous trees Grass and coniferous trees Grass and mixed trees Pavement Farmland Forested Bare Other
Forest nearby	A group of 10 or more trees that grow close enough to obscure a bird’s eye view of the ground beneath; coded as “present” when forest is within 0.10 mi	Present Absent
Farm nearby	Patch of land (field) greater than 0.5 acres that appears to grow crops or that is not forested, grassed or cultivated for reasons beyond creating produce; coded as “present” when field is within 0.10 mi. (Note: grassy, large, open areas coded as park, not farm.)	Present Absent

\*On the “map” view option of Google Maps, parks are designated in shades of green.

encountered in previous studies.<sup>3,5,12-16</sup> Linear distances were calculated via map view. Variables of interest were explored as defined and summarized in Table 1. Nearby natural features were explored for every case and control subject. For nearby businesses, every type of business was explored for the first 35 blastomycosis cases. For the remainder of cases, and all of the controls, business types rarely or not found in the first 35 blastomycosis cases were not sought.

### Statistical Analysis

Minitab® statistical software (State College, PA) was used for data analysis. Basic descriptive and summary statistics were calculated. Categorical data were analyzed using chi-square tests with Yates’ correction. Continuous variables were analyzed using two-sample t-tests.

Stepwise regression (for significant predictors) followed by binary logistic regression was used for multivariable analysis of blastomycosis cases versus CAP controls for variables found statistically significant on univariable analysis. Odds ratios were calculated. Significance of associations was defined by P-value less than 0.05. Case and control home addresses by Wisconsin ZIP code were compiled into maps using ArcGIS 10 geographic information system software (Esri, Redlands, CA).

### RESULTS

From July 2007 to July 2015, 193 laboratory-confirmed blastomycosis cases were identified. The calculated annual incidence rate based on this eastern Wisconsin health system’s patient population (i.e. 1.2 million distinct patients per year) is 2.01 cases/100,000 persons,

which is consistent with previous estimations.<sup>5</sup> Of note, this is not a community-based population incidence rate.

Compared to CAP controls, adult blastomycosis cases were significantly younger (47.7 vs. 55.3 years,  $P < 0.0001$ ) and more likely to be male (67.9% vs. 45.6%,  $P < 0.0001$ ). Blastomycosis cases differed from controls regarding distribution of race/ethnicity (cases: white 77%, black 11%, Hispanic 7%, other 5%; vs. controls: white 90%, black 5%, Hispanic 5%) in that cases were more apt than controls to be black ( $P = 0.024$ ) or nonwhite ( $P = 0.0004$ ).

Interpretable occupations were listed for 85 cases and 152 controls. Cases were more likely than controls to be machinists, automobile workers/mechanics or construction workers than all other occupations (32.7% vs. 7.2%,  $P < 0.0001$ ). Additionally, cases were more likely than controls to have one of the following occupations — machinist, automobile worker/mechanic, construction worker, postal or truck driver, and machinery- or auto-related occupation such as mechanical engineer or automobile sales — than any other occupation (61.2% vs. 32.9%,  $P < 0.0001$ ).

A total of 159 cases and 226 controls had addresses that were not post office box numbers and were locatable

on Google Maps. Most subjects lived in neighborhoods technically classified as urban or suburban. The breakdown of this distribution did not differ between blastomycosis subjects and CAP controls (blastomycosis: urban 82%, suburban 8%, rural 8%, farm 2% vs. controls: urban 81%, suburban 9%, rural 5%, farm 5%). A number of geographic and surface geologic differences, at various distances, were seen between cases and controls when these variables were subjected to univariable analysis (Table 2). Interestingly, home sites of control subjects were significantly more likely to be within a quarter-mile of a waterway than case home sites (54.4% vs. 43.4%,  $P = 0.04$ ); however, cases were significantly more likely than controls to have water frontage (17.6% vs. 7.5%,  $P = 0.004$ ). Cases were more likely than controls to be in close proximity to forests, farm fields, parks, auto-related businesses and places of worship.

Following multivariable modeling, significant remaining predictors of blastomycosis cases, as compared to CAP controls, included male sex, younger age, nonwhite race/ethnicity, occupation in machinery- or auto-related businesses or as postal or freight drivers (as compared to all other occupations), and home sites within 0.1 miles of a park, forest or farm field (Table 3).

Figure 1 illustrates the geographic distribution of Wisconsin-only case and control subjects.

**Table 2.** Significant geographic or surface geologic predictors on univariable modeling: blastomycosis cases vs. CAP controls

Characteristic*	Cases	Controls	P
Water frontage	17.6% (n=28)	7.5% (n=17)	0.004
Forest (within 0.10 mi)	37.1% (n=59)	20.8% (n=47)	0.0006
Farm field (within 0.10 mi)	30.2% (n=48)	15.9% (n=36)	0.001
Property size (>0.5 acres)	30.4% (n=48)	14.2% (n=32)	0.0002
Property size (>2 acres)	20.9% (n=33)	6.2% (n=14)	<0.0001
Within 0.1 mi of auto business	14.5% (n=23)	3.5% (n=8)	0.0002
Within 0.25 mi of auto business†	35.9% (n=57)	19.4% (n=44)	0.0005
Within 0.1 mi of park	32.7% (n=52)	22.6% (n=51)	0.036
Within 0.25 mi of worship	44.7% (n=71)	33.2% (n=75)	0.030
Within 0.1 mi of park/forest/farm	54.9% (n=106)	39.6% (n=99)	0.002
Machinist/autoworker/construction	31.8% (n=27)	7.2% (n=11)	<0.0001
Above occupation, other machinery/auto-related employment, or postal/truck driver	61.2% (n=52)	32.9% (n=50)	<0.0001

\*See Table 1 for characteristic descriptions/definitions.

†Distribution of nearby automobile-related businesses, as delineated in Table 1, did not differ between cases and controls (data not shown).

CAP, community-acquired pneumonia.

**Table 3.** Significant predictors on multivariable modeling: blastomycosis cases vs. CAP controls

Predictor	P	Odds ratio
Male	0.001	3.44
Age	<0.0001	0.95*
Nonwhite race	<0.0001	6.25
Within 0.1 mi of park/forest/farm	0.011	2.38
Machinist/autoworker/construction	<0.0001	6.89
Above occupation, other machinery/ auto-related employment, or postal/truck driver†	0.03	2.86

\*Risk decreases 5% for every additional year of age.

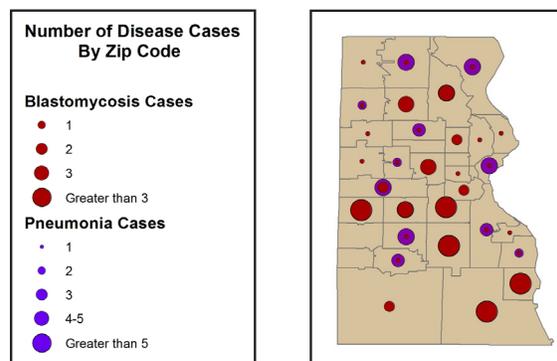
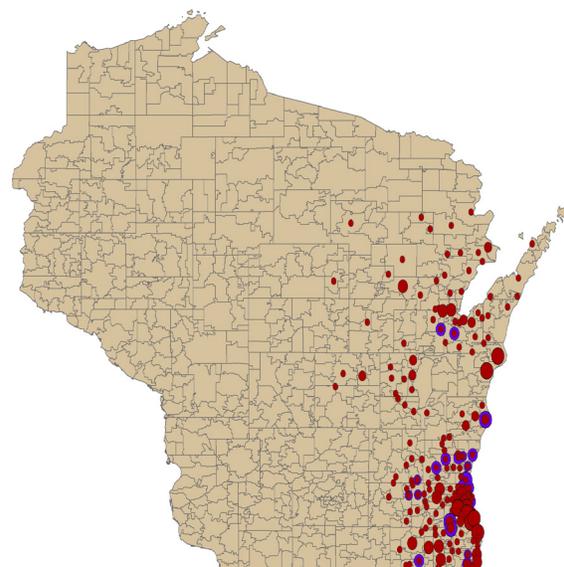
†When placed in multivariable model instead of the variable listed immediately above, significance and odds ratios of other items were not significantly affected.

CAP, community-acquired pneumonia.

Blastomycosis cases were more widely dispersed throughout the eastern Wisconsin catchment area of our integrated health system than CAP controls, whereas the latter were concentrated around the urban centers of eastern Wisconsin. Overall, 37.1% of case and 44.0% of control home addresses were within the urban counties of Milwaukee and Waukesha, an insignificant difference (P=0.18).

## DISCUSSION

This epidemiologic survey revealed several important geodemographic associations between patients with laboratory-diagnosed blastomycosis and those diagnosed with CAP. Many of these associations were anticipated, a few were not. Male predominance of blastomycosis cases, and a normal distribution of age around middle-aged adults, have been recognized in many endemic regions for decades<sup>1</sup> and in Northern Wisconsin over the past 35 years.<sup>10</sup> Among adults, CAP is considered a disease of the elderly with equal sex and racial distribution, although good community-based data is lacking.<sup>35,36</sup> Prior studies have inconsistently suggested an increased incidence of blastomycosis in blacks and certain other nonwhite persons,<sup>37,38</sup> and higher age-adjusted mortality rates in these groups.<sup>39</sup> Recent studies have suggested differing clinical features of blastomycosis among different human genetic and ethnic groups.<sup>8,40</sup>



**Figure 1.** Blastomycosis versus pneumonia cases, Wisconsin 2007–2015. Maps of the geographic distribution of blastomycosis cases and control subjects with community-acquired pneumonia in eastern Wisconsin and Milwaukee County (inset). Blastomycosis cases were more widely dispersed throughout the eastern Wisconsin catchment area of the studied integrated health system than pneumonia controls.

In Vilas County, in rural northern Wisconsin, human and dog blastomycosis cases were associated with close proximity to waterways,<sup>13,16</sup> perhaps most especially lower elevation lakes.<sup>12</sup> In urban Milwaukee County, blastomycosis cases were most commonly associated with open inland water sites, followed by the Lake Michigan shoreline, compared to highly organized and controlled inland waterways.<sup>5</sup> The present study reveals a paradox, on univariable analysis, whereby home sites of control subjects were more apt to be within a quarter-mile of a waterway compared to blastomycosis cases, whereas blastomycosis case home properties were more apt to have water frontage. The eastern Wisconsin

location of this study, particularly with respect to the highly urbanized areas (where CAP controls were clustered), includes the Lake Michigan shoreline as a dominant geographic feature. This is not true in Vilas County. Perhaps the housing layouts for our selected controls are not geographically random such that the control group has a predominance of quarter-mile waterway proximity due to population density. The association with water frontage in our present study is reminiscent of the association of dog blastomycosis cases with very close waterway proximity in a previous study of Eagle River, a municipality in rural northern Wisconsin.<sup>15</sup> Property water frontage or very close waterway proximity that would invite human or animal contact with the shoreline may be paramount.

Certainly, many outbreak and endemic cases of blastomycosis are in or near forestation (or rural areas including farms).<sup>19</sup> This is true involving Vilas County,<sup>16,31</sup> however, statistical association of forests with cases versus controls was not seen, perhaps because of the extensive forestation in the region.<sup>13</sup> In the present study, multivariable analysis revealed significantly increased odds of a blastomycosis home site being in close proximity to a park, forest or farm field. Perhaps these features, often considered to be more typical of rural areas but sometimes found in association with urban and suburban areas, provide important ecological habitat for *Blastomyces* to persist or temporarily thrive such that spores of the fungus blow into or propagate in the case property,<sup>10,11,21</sup> or the resident is exposed to the fungus during a short walk or soil-disturbing activity. Overall, the distribution of blastomycosis case home sites in eastern Wisconsin in our study matched closely with a map of the predicted geographic distribution of cases in this region based on ecologic niche modeling.<sup>41</sup>

Our study has shown an association between blastomycosis and occupation as a machinist, autoworker, construction worker, truck driver or in other machinery/auto-related businesses on both univariable and multivariable analyses. Residence in close proximity to auto-related businesses was associated on univariable analysis only. As reviewed elsewhere in this issue,<sup>24</sup> many studies, but not all,<sup>42</sup> found outdoor occupations made up a minority of blastomycosis cases. There have been reports of blastomycosis cases in autoworkers based on short case series or case

studies,<sup>37,43-45</sup> but no systematic investigation of this connection. Whether auto-related businesses afford opportunities for workplace exposure to *Blastomyces*, or whether this association simply reflects persons who disproportionately encounter the fungus during home or recreational activities, is unclear.

Based on county level data, blastomycosis hospitalization was associated with increased levels of mercury and decreased levels of copper in the soil.<sup>3</sup> One recent study documented significant levels of heavy metal contamination within auto repair workshops (likely containing dirt floors). However, this study was conducted in Nigeria, where regulations are substantially different than in the United States.<sup>46</sup> In the early 1990s, the potential for substantial heavy metal and both organic and inorganic chemical pollution surrounding automobile facilities in the United States was recognized.<sup>47</sup> Concern for accidental spills remains a concern.<sup>48</sup>

*Blastomyces* has been shown to tolerate a variety of harsh substances.<sup>19,21,22</sup> One can speculate that human or machinery “tracking,” or “washout” of heavy metals or chemicals onto nearby soil (adjacent to parking lots, etc.), could lead to a microenvironment that favors growth of *Blastomyces*. Regardless, occupational risk for blastomycosis, beyond that of obvious soil-disturbing activities, should not be discounted. A 2009 study of 112 blastomycosis patients and 118 neighborhood controls revealed that having a coworker with blastomycosis was an independent risk factor for the disease.<sup>42</sup> Further investigation of associated occupations seems warranted.

### Study Limitations

The retrospective nature of the present study has the inherent limitation of reliance on data collected for clinical or registration purposes being complete and accurate. This was likely only significantly limiting for data regarding occupation. Additionally, important variables may not have been explored. This study primarily investigated home sites of blastomycosis cases. The authors attempted to use the home address most closely associated with the occurrence of the index illness, however, it is possible that certain addresses did not reflect the location at the time of disease exposure or occurrence. Such discrepancy could have occurred for both case and control subjects, but presumably to a limited extent.

One might suggest that observation of home sites using Google Maps is no substitute for personally visiting the home site and interviewing the subject, and that features observed at the time of acquisition of the particular satellite map may have differed from that at the time of case exposure or occurrence, perhaps due to temporal or seasonal differences. Some important nearby businesses or other built environmental features may not have been observed on existing maps. It was not possible to make a direct link between cases and occupations at particular facilities close to (or distant from) their homes. Similarly, we were unable to determine if particular auto-related businesses were outdoor or open facilities (i.e. exposed to the elements). Certainly, these are all valid concerns. Nonetheless, with limited resources, this approach was an inexpensive way to objectively view and measure the surface features of the involved home sites.

## CONCLUSIONS

In predominantly urban/suburban eastern Wisconsin, blastomycosis occurs less frequently than in rural northern Wisconsin, yet the disease burden is not trivial. Having nearby natural, open or nondomicile features such as park land, forests or fields may increase the risk of a home site being associated with blastomycosis. Additional epidemiologic and environmental studies (hampered, of course, by the difficulty in isolating *Blastomyces* from the environment<sup>30</sup>) are required to determine if automobile/machinery-related occupations or nearby businesses increase the risk for acquisition of blastomycosis. Further elucidation of the environmental determinants of *Blastomyces* distribution and propagation could lead to more specific preventive recommendations.

### Patient-Friendly Recap

- Blastomycosis is a fungal infection, primarily of the lungs.
- In rural Wisconsin, it is likely most often acquired by people living near waterways.
- The authors identified cases of blastomycosis contracted by people living in more urbanized areas of the state and studied the landscape surrounding their homes.
- They found that homes near parks, forested lots or urban/suburban fields as well as employment by machinery- or auto-related businesses may increase likelihood of blastomycosis occurrence.

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## Conflicts of Interest

None.

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