

Detection of Bacteriuria by Canine Olfaction

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Background. Urinary tract infections (UTIs) are a significant medical problem, particularly for patients with neurological conditions and the elderly. Detection is often difficult in these patients, resulting in delayed diagnoses and more serious infections such as pyelonephritis and life-threatening sepsis. Many patients have a higher risk of UTIs because of impaired bladder function, catheterization, and lack of symptoms. Urinary tract infections are the most common nosocomial infection; however, better strategies are needed to improve early detection of the disease.

Methods. In this double-blinded, case-control, validation study, we obtained fresh urine samples daily in a consecutive case series over a period of 16 weeks. Dogs were trained to distinguish urine samples that were culture-positive for bacteriuria from those of culture-negative controls, using reward-based clicker and treat methods.

Results. Samples were obtained from 687 individuals (from 3 months to 92 years of age; 86% female and 14% male; 34% culture-positive and 66% culture-negative controls). Dogs detected urine samples positive for 100 000 colony-forming units/mL *Escherichia coli* (N = 250 trials; sensitivity 99.6%, specificity 91.5%). Dilution of *E coli* urine with distilled water did not affect accuracy at 1% (sensitivity 100%, specificity 91.1%) or 0.1% (sensitivity 100%, specificity 93.6%) concentration. Diagnostic accuracy was similar to *Enterococcus* (n = 50; sensitivity 100%, specificity 93.9%), *Klebsiella* (n = 50; sensitivity 100%, specificity 95.1%), and *Staphylococcus aureus* (n = 50; sensitivity 100%, specificity 96.3%). All dogs performed with similarly high accuracy: overall sensitivity was at or near 100%, and specificity was above 90%.

Conclusions. Canine scent detection is an accurate and feasible method for detection of bacteriuria.

Keywords. bacteriuria; canine scent detection; *E coli*; spinal cord injury; urinary tract infection.

People of all ages develop bacteriuria and urinary tract infections (UTIs), which causes significant morbidity and healthcare costs [1]. In the United States alone, UTIs account for approximately 10 million physician office visits each year. In 2000, the estimated cost to diagnose and treat UTIs exceeded \$3.5 billion [2, 3]. Most UTIs occur in young women and are easily treated; however, for certain populations, UTIs can be complicated and life-threatening if left untreated.

Individuals with neurological conditions such as spinal cord injuries (SCIs) are at a greater risk of developing complications. Spinal cord damage hampers bladder emptying and blocks symptoms that normally signal infection. In these patients, UTIs may progress rapidly and are the leading cause of hospitalization [4]. Patients with SCI are substantially more likely than ambulatory patients to develop bladder cancer at an earlier age, and they are often diagnosed at more advanced stages of the disease [5]. The elderly, hospitalized patients,

and pregnant women also have a higher risk of developing complications.

Urinary tract infections are the most common hospital-acquired infections for all patients [6]. Up to 20% of hospitalized patients receive urinary catheters, increasing UTI risk by 5% per hospitalization per day. Almost all patients with indwelling-catheters develop frequent UTIs, and up to 40% of hospital-acquired infections are catheter-associated [7]. These infections are caused by multiple organisms including *Escherichia coli* (found in 80% of UTIs), *Staphylococcus aureus*, *Proteus*, *Enterococcus*, *Pseudomonas*, *Enterobacter*, *Klebsiella*, and *Candida*. Given the prevalence of UTIs, their complications, and increasing drug therapy resistance, improved early detection methods are needed.

The most commonly used treatment for UTIs are antimicrobial agents (eg, trimethoprim-sulfamethoxazole, quinolones, or nitrofurantoin). However, frequent and prolonged drug therapy leads to multidrug-resistant infections [8, 9], pyelonephritis, and sepsis [8]. The incidence of drug-resistant UTIs has increased in recent years [10], potentially leading to a post-antibiotic era [11].

Dogs' olfactory acuity is over 100 000 times stronger than humans, and they are able to detect odors in parts per trillion [12]. Dogs' superior olfactory capabilities have served humans in an impressive number of ways: eg, finding missing persons and criminals [13], detecting bombs and drugs, and, more recently, detecting cancer [14, 15, 16].

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Sniffing urine is an innate behavior in dogs. It is known to serve several functions: identification of self and others [17], territorial marking [18], and identifying fertility [19]. This behavior may also be the dogs' way of evaluating the health status of other dogs, thereby predisposing dogs to exceptional accuracy in identifying disease in humans by sniffing urine samples.

With severe infection, prompt treatment minimizes morbidity and mortality [20]. In many patients, early diagnosis is difficult to achieve, and urine culture results cause further delays, taking up to 48 hours for laboratory tests to be completed. Trained dogs may present a novel method for early UTI detection, and this technique is potentially relevant to people with neurological impairment, hospitalized patients, and the elderly. Our objective was to determine whether canines could be trained to distinguish the odor of urine samples culture-positive for bacteria from culture-negative control samples.

METHODS

Patient Eligibility

Eligible subjects were male or female without age restrictions. "Cases" were bacterial-culture positive (>100 000 colony-forming units [cfu]/mL), and "controls" were bacterial-culture negative. We excluded samples with visible blood, or those from patients receiving chemotherapy or radiopharmaceuticals. There were no other restrictions.

Sample Collection

Urine samples were obtained from the Clinical Laboratories of Hawaii in a consecutive case series. Samples were sent from the collection site (hospital or doctor's office) to the laboratory, where a urine culture was performed. This process took 48 hours. The transport time from the laboratory to the training facility took approximately 6 hours, and samples were kept under continuous refrigeration until used.

Analysis

Our primary outcome was the dogs' sensitivity and specificity in detecting *E coli*-positive urine samples. Our secondary outcomes were as follows: (1) sensitivity and specificity in detecting *E coli*-positive urine samples diluted with distilled water to 1% and 0.1% concentration; and (2) sensitivity and specificity in detecting samples that tested positive for other bacteria, eg, *Klebsiella*, *Enterococcus*, and *S. aureus*.

Human Subjects Concerns

An institutional review board (IRB), Hawaii Pacific Health Research Institute, ruled the study exempt from review because samples were gathered during the course of routine clinical care and were to be discarded. The study involved no more than minimal risk to subjects, and the consent waiver did not affect subjects' rights and welfare.

Institutional Animal Care and Use Committee

A US Public Health Service-compliant Institutional Animal Care and Use Committee (IACUC) was established and consisted of 5 members: 1 veterinarian chairperson, 1 institutional member, and 3 lay members representing general community interests in the proper care and treatment of animals [21]. The IACUC approved the training facility and study protocol.

Training Room

The training room was 9.14 meters squared, ventilated on 3 sides with overhead and natural lighting, and temperature-controlled (21–26°C). The floor was steam-cleaned at the end of each training day. No food was allowed in the training room. To minimize contamination by other odors, access to the training room by other people or dogs was disallowed for the duration of the study.

Laboratory Room

The laboratory room (3.04 by 3.66 meters) was adjacent to the training room and had a privacy window allowing researchers to observe blinded runs. No food or drinks were allowed in the laboratory room, and samples were stored in a refrigerator (1.11–3.33°C).

Technicians wore gloves to handle samples and changed gloves between handling case and control samples. Subject identification (ID) numbers were sequential and assigned by the laboratory. Samples were removed from the refrigerator prior to the run in which they were used and discarded immediately after each session.

Scent Detection Boxes

Urine (1 mL) was placed in a 2-mL CryoTube vial (Thomas Scientific) and then placed in a tray. These trays were then placed in 5 separate plastic scent detection boxes, which were lined up on the floor at 65.0 cm apart. The boxes allowed air circulation around the urine samples, which could not be reached by the dog's nose or mouth. The boxes were 30.5-cm square and 25.4-cm tall with a 5.0-cm circular opening at the top. The boxes were also of sufficient weight to prevent tipping, and each box had a 7.6-cm high base and snug-fitting removable lid (Figure 1).

Personnel

Research staff included dog handlers, sample handlers, and data recorders. Dog handlers worked with 1 dog at a time, leading them on or off leash into the room towards the lineup of boxes. Dogs were encouraged to approach and sniff the boxes with a verbal cue of "go find". The sample handler, the only person who knew the identity of the samples, was stationed in the laboratory room. They observed runs through a privacy window in the laboratory room. A data recorder was hidden behind a solid curtain in the far corner of the training room during double-blinded runs, and he/she observed and recorded results on paper and video.

Training

Dog training took place at Assistance Dogs of Hawaii (Makawao, HI) 4 days a week. Five dogs were selected to participate:



Figure 1. Sam approaching a scent detection box.

Labrador and Golden Retrievers ranging in age from 1 to 8 years old with various levels of prior behavioral training but no scent training. Handheld clickers and food rewards were used as positive reinforcement if the dog correctly alerted to infected urine samples, and training lasted for 8 weeks.

We used a previously published experimental design with 1 case and 4 control samples placed in scent detection boxes in a row on the training room floor. During the training phase, the dogs learned to ignore the hundreds of other odors found in urine and focus on locating only the samples that tested positive for bacteria. The training phase was unblinded, with the sample handler, data recorder, and dog handler all aware of the identity of each sample in the lineup (case or control). During the training phase, samples were presented to the dogs in 5 sequential stages (see Table 1) [14]. At each stage, dogs were rewarded for correct responses.

Training Phases

There were 5 training stages in this phase. In Stage 1, the target box contained the case sample and a food treat, but control boxes contained empty vials. When the dogs sniffed the case sample

Table 1. Sequential Stages of Dog Training and Testing

Phase	Location of Case Sample Among 5 Stations	Contents of Station With Target Stimuli	Contents of Other 4 Stations	Sequence of Events at the Station With Case Sample	Location of Case Sample Known by:
Training					
Stage I	Randomly chosen	Case sample Food	Blank vials	1. Sniffing 2. Natural alert 3. Clicker 4. Praise 5. Food reward	Sample handler Data recorder Dog handler
Stage II	Randomly chosen	Case sample Food	Blank vials	1. Sniffing 2. Trained alert (sit) 3. Clicker 4. Praise 5. Food reward	Sample handler Data recorder Dog handler
Stage III	Randomly chosen	Case sample	Water	1. Sniffing 2. Trained alert (sit) 3. Clicker 4. Praise 5. Food reward	Sample handler Data recorder Dog handler
Stage IV	Randomly chosen	Case sample	Control sample diluted with water	1. Sniffing 2. Trained alert (sit) 3. Clicker 4. Praise 5. Food reward	Sample handler Data recorder Dog handler
Stage V	Randomly chosen	Case sample	Full-strength control sample	1. Sniffing 2. Trained alert (sit) 3. Clicker 4. Praise 5. Food reward	Sample handler Data recorder Dog handler
Testing					
Single-blinded trials	Randomly chosen	Case sample	Control sample	1. Sniffing 2. Trained alert (sit) 3. Clicker (sample handler) 4. Reward (dog handler)	Sample handler Data recorder
Zero trials	Case sample not present	Control sample	Control sample	1. Sniffing 2. No clicker or food reward if dog sits at any sample	Sample handler
Double-blinded trials	Randomly chosen	Case sample	Control sample	1. Sniffing 2. Trained alert (sit) 3. Clicker (sample handler) 4. Reward (dog handler)	Sample handler

and demonstrated a natural alerting behavior, the trainer activated the clicking device and provided a food reward. Stage 1 lasted for 2 days. In Stage 2, the target box contained the case sample and a food treat, and control boxes were empty. Dogs were taught to sniff the boxes and sit in front of the case sample. Stage 2 lasted for 2 days. In Stage 3, the target box contained the case sample, and control boxes contained water. Dogs were taught to sniff the boxes and sit in front of the case sample. Stage 3 lasted for 1 day. In Stage 4, the target box contained the case sample, and control boxes contained diluted control samples. Dogs were taught to sniff the boxes and sit in front of the case sample. Stage 4 lasted for 1 day. Finally, in Stage 5, the target box contained the case sample, and control boxes contained full-strength control samples. Dogs were taught to sniff the boxes and sit in front of the case sample. Stage 5 lasted for 6 weeks. When accuracy exceeded 90%, single-blinded runs were introduced.

Testing

In the single- and double-blinded testing of the dogs, all new case and control samples were used, and none of these had been used during the training phase. This process ensured that the dogs had not merely learned the scent of samples from specific patients. A random number table was used to determine the order of the runs and entry of samples in each row. Each test run contained 1 case and 4 control samples. New boxes were used for each test run to ensure the dogs did not receive clues from the previous dogs.

The dogs were run from left to right, from Station 1 through 5, and the placement of case samples were determined by a random number table for each run. The sample handler placed samples into boxes and at the stations. The dog handler was blinded to the sample placement. To provide ongoing reinforcement for correct alerting behavior, the sample handler observed the runs from behind the privacy window in the closed laboratory room and “clicked” when the dogs sat in front of a case sample. The dog handler would then reward the dog with a treat. The testing phase took place over a 10-week period and included the following. (1) Single-blinded testing was done, in which the data recorder (but not the dog handler) knew the identity of samples. Dogs sniffed the lineup and alerted by sitting in front of the case samples. (2) “Zero trials” used only control samples, to ensure dogs were not simply alerting to earn a reward. (3) Double-blinded validation, which were blinded to both the data recorder and the dog handler. Dogs sniffed the lineup, and the dog handler called out the station number (1 through 5) at which the dog sat, if any. This was confirmed by the data recorder.

Sample status (case vs control) was not decoded until all dogs completed testing. The dogs were taught to work off leash so that during double-blinded runs they could work independently. Data will be retained for 5 years after study completion.

Testing Other Types of Bacteria

The dogs were initially trained and tested using case samples that contained *E coli* bacteria, which causes most UTIs. Case samples

were then introduced that contained other types of bacteria. The dogs accurately identified samples containing *Klebsiella*, *Enterococcus*, and *S. aureus*, without additional training. It may be possible for dogs to differentiate between different types of bacteria, but that was beyond the scope of this pilot project.

Testing of Diluted Samples

The dogs were tested on *E coli* samples that were diluted to 1.0% and 0.1% with distilled water. The dogs correctly distinguished between diluted case and control samples with the same accuracy as full-strength samples, without additional training, which suggests that they may be able to identify early stages of infections. This may be relevant for 320 catheterized patients, whose threshold of clinical significance is much lower than the general threshold of bacterial count exceeding 100 000 cfu/mL [22].

Data Management

During training runs, the sample handler announced location of samples (Stations 1, 2, 3, 4, or 5), sample box letter (a, b, c . . . x), ID number of sample, and identity of sample (case vs control). The data recorder entered that information on paper forms.

During double-blinded testing runs, the sample handler, stationed in the laboratory room, was the only one who knew the identity of the samples and location of the target sample. This information was recorded electronically at the end of each day. Each testing run was video-recorded and data were audited daily.

Classification of Dogs' Response

When the dogs located a case sample, they alerted the dog handler by sitting. Dog handlers were instructed to declare only a clear and distinct alerting response by the dog sitting directly in front of a specific sample. Correct responses by the dogs were (1) sniffing and sitting in front of a case sample (true positive) and (2) sniffing but not sitting in front of control samples (true negative). Incorrect responses were (1) sitting in front of a control sample (false positive) and (2) not sitting in front of a case sample (false negative). An apparent hesitation or a partial sit signified a nonalert. At the end of each run, the dog handler called out the results: “sniffed at [which stations]” and “alerted at [which stations]”. Results were confirmed and entered by the data recorder.

Randomness of Case Sample Placement

To ensure the dogs were not learning to alert to a particular box or at a particular station, the placement of the scent detection boxes (a–x) containing the case samples at each of the 5 stations (1–5) was determined using a random number table. At each of the 5 stations, sample handlers randomly rotated among the 24 different scent detection boxes. Statistical testing confirmed each trial was an independent event, so that each location would have a 20% probability of holding a case sample without regard to prior sessions (χ^2 test, $P > .05$ for all stations).

Table 2. Canine Scent Detection of Bacteriuria: Sensitivity and Specificity by Bacteria Type^a

Dog	Sample Type	Dog's Indication			Sensitivity	Specificity
		Sit	No Sit	Total		
<i>Escherichia coli</i>	Case	249	1	250	99.6%	91.5%
	Control	78	840	918		
	Pearson $\chi^2 = 809.0, P < .001$					
<i>E coli</i> 1%	Case	50	0	50	100.0%	91.1%
	Control	13	133	146		
	Pearson $\chi^2 = 141.7, P < .001$					
<i>E coli</i> 0.1%	Case	50	0	50	100.0%	93.6%
	Control	9	132	141		
	Pearson $\chi^2 = 151.5, P < .001$					
<i>Enterococcus</i>	Case	50	0	50	100.0%	93.9%
	Control	9	138	147		
	Pearson $\chi^2 = 156.7, P < .001$					
<i>Klebsiella</i>	Case	50	0	50	100.0%	95.1%
	Control	7	135	142		
	Pearson $\chi^2 = 160.1, P < .001$					
<i>Staphylococcus aureus</i>	Case	50	0	50	100.0%	96.3%
	Control	4	105	109		
	Pearson $\chi^2 = 141.8, P < .001$					

^a Samples not sniffed by dogs were not included in the analysis; therefore, group totals may be different.

RESULTS

Subjects

Clinical Laboratories of Hawaii provided samples from 687 individuals (86% female and 14% male). Ages ranged from 3 months to 92 years. Samples included both inpatients and outpatients. Four hundred fifty-six samples (66%) were from subjects with completely negative urine cultures (controls), and 231 (34%) samples were from subjects with positive urine cultures (cases) verifying bacteriuria (>100 000 cfu/mL): *E coli* (n = 191), *S. aureus* (n = 11), *Enterococcus* (n = 10), and *Klebsiella* (n = 19) (Table 2).

Diagnostic Accuracy

In double-blinded conditions, the dogs detected urine samples positive for *E coli* with sensitivity of 99.6% and specificity of 91.5%. Dilution of *E coli* samples with distilled water did not affect accuracy at either 1.0% (sensitivity 100%, specificity 91.1%) or 0.1% (sensitivity 100%, specificity 93.6%). Accuracy was similar in identifying urine samples that were culture-positive for *Enterococcus* (sensitivity 100%, specificity 93.9%), *Klebsiella* (sensitivity 100%, specificity 95.1%), and *S. aureus* (sensitivity 100.0%, specificity 96.3%) (Table 2). For all 5 dogs, sensitivity range was 99.0% to 100%, and specificity range was 90.1% to 94.7% (Table 3).

DISCUSSION

Canines can be taught to accurately discriminate between culture-positive and culture-negative urine samples. This method

Table 3. Canine Scent Detection of Bacteriuria: Sensitivity and Specificity by Individual Dog^a

Dog	Sample Type	Dog's Indication			Sensitivity	Specificity
		Sit	No sit	Total		
Abe: 1-year-old Labrador/Golden Retriever	Case	100	0	100	100.0%	94.7%
	Control	17	304	321		
	Pearson $\chi^2 = 340.8, P < .001$					
Astro: 1-year-old Labrador/Golden Retriever	Case	100	0	100	100.0%	92.7%
	Control	21	266	287		
	Pearson $\chi^2 = 296.4, P < .001$					
Sadie 3-year-old Labrador Retriever	Case	100	0	100	100.0%	90.1%
	Control	32	292	324		
	Pearson $\chi^2 = 289.5, P < .001$					
Sam 8-year-old Golden Retriever	Case	100	0	100	100.0%	94.5%
	Control	19	327	346		
	Pearson $\chi^2 = 344.6, P < .001$					
Scout 3-year-old Labrador Retriever	Case	99	1	100	99.0%	90.5%
	Control	31	294	325		
	Pearson $\chi^2 = 288.3, P < .001$					

^a Samples not sniffed by dogs were not included in the analysis; therefore, group totals may be different.

was also an accurate means of diagnosis for urine samples containing *E coli*, *Enterococcus*, *Klebsiella*, and *S. aureus*. Sensitivity and specificity were equally high for samples diluted with distilled water to either 1.0% (1000 cfu/mL) or 0.1% (100 cfu/mL). The results suggest that dogs may be taught to accurately detect bacterial infections at an early stage when less aggressive therapy is needed. In our dilution experiments, we observed that the dogs were able to detect very low bacterial counts. Detecting negative cultures may also be clinically useful and help avoid overuse of antibiotic therapy.

One month after the study was completed, 1 of the dogs (Abe) spontaneously alerted to a person visiting the training center. The patient had been feeling ill, but had not suspected a UTI. Based on Abe's alerting behavior, the patient had a medical exam and a urine culture was performed the next day, and physicians confirmed bacteriuria and a clinical diagnosis of UTI.

Limitations

In this IRB-exempt trial, the covariate data were limited to age, gender, and specific organism identified by urine culture. It is possible that there was unmeasured confounding by factors other than bacteria. Whether or not comorbid conditions were present, these trained dogs did distinguish accurately by scent those urine samples that were culture-positive from those that were culture-negative. Clinical data were not included; therefore, clinical correlation of the bacteriuria status of the samples was not possible.

Case samples were used only once in the testing phase, whereas control samples were used throughout each day of testing. It is possible that dogs may learn to identify that which is new in a lineup. If this occurred, the first runs of each day (with

all new samples) would have lower accuracy rates than the subsequent runs. However, statistical testing that confirmed the accuracy rates for the first runs of each day were identical to overall accuracy rates. In future work, we plan to use new control samples for each run.

Future Directions

This team is the first to publish data on canine scent detection of bacteriuria. Dogs' ability to detect low levels of bacteriuria suggests the possibility of dogs providing early detection of UTIs. Existing methods to detect UTIs usually require the individual to seek care and request a test as a result of symptoms. In persons with neurological impairment such as SCI, this is difficult because symptoms are often not present. This truly noninvasive diagnostic method to identify patients with UTIs has a unique potential for several practical applications. The populations most often affected by complicated UTIs (people with disabilities, hospitalized patients, and the elderly) may benefit from assistance from dogs that could be trained to provide early detection of UTIs.

Future work could address additional questions that were not within the scope of this study, including testing samples containing mixed bacterial cultures, differentiating between types of bacteria, and finding the dogs' lower limit of detection. Assessing negative predictive values for clinical syndromes could also be an important aim of future studies.

CONCLUSIONS

Dogs' ability to detect bacteriuria suggests the feasibility of using canine scent detection to identify other types of bacterial infections through biological samples. For example, dogs may be trained to identify bacterial pneumonia through breath samples. Dogs may also be able to locate other types of bacteria in hospitals such as methicillin-resistant *S. aureus* and *Clostridium difficile*, similar to a proof-of-principle study demonstrating that a dog could detect *C difficile* in patients' hospital rooms and stool samples [23]. Our results also suggest that medical equipment could be developed to provide early detection of bacterial infections, similar to the "electronic noses" recently designed to detect prostate cancer [24], and bacteria in blood samples [25].

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References

1. Orenstein R, Wong ES. Urinary tract infections in adults. *Am Fam Physician* **1999**; 59:1225–34.
2. National Kidney & Urologic Diseases Information Clearinghouse (NKUDIC). Kidney and Urologic Diseases Statistics for the United States. Available at: <http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm>. Accessed 25 February 2012.
3. Albert X, Huertas I, Pereiro II, et al. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* **2004**; 3: CD001209.
4. Cardenas DD, Hoffman JM, Kirshblum S, McKinley W. Etiology and incidence of rehospitalization after traumatic spinal cord injury: a multicenter analysis. *Arch Phys Med Rehabil* **2004**; 85:1757–63.
5. Welk B, McIntyre A, Teasell R, et al. Bladder cancer in individuals with spinal cord injuries. *Spinal Cord* **2013**; 51:516–21.
6. Klevens RM, Edwards JR, Andrus ML, et al. Dialysis surveillance report: national healthcare safety network (NHSN)-data summary for 2006. *Semin Dial* **2008**; 21:24–8.
7. Warren JW. Catheter-associated urinary tract infections. *Infect Dis Clin North Am* **1997**; 11:609–22.
8. Manges AR, Johnson JR, Foxman B, et al. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. *The N Engl J Med* **2001**; 345:1007–13.
9. Rahn DD. Urinary tract infections: contemporary management. *Urol Nurs* **2008**; 28:333–41.
10. Levison ME, Mallela S. Increasing antimicrobial resistance: therapeutic implications for enterococcal infections. *Current Infect Dis Rep* **2000**; 2:417–23.
11. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* **2013**; 13:1057–98.
12. Walker BD, Walker JC, Cavnara PJ, et al. Naturalistic quantification of canine olfactory sensitivity. *Appl Anim Behav Sci* **2006**; 97:241–54.
13. Ensminger J, Jezierski T, McCulloch M. Scent Identification in Criminal Investigations and Prosecutions: New Protocol Designs Improve Forensic Reliability. Available at: <http://ssrn.com/abstract=1664766> or <http://dx.doi.org/10.2139/ssrn.1664766>. Accessed 24 August 2010.
14. McCulloch M, Jezierski T, Broffman M, et al. Diagnostic accuracy of canine scent detection in early- and late-stage lung and breast cancers. *Integr Cancer Ther* **2006**; 5:30–9.
15. Ehmann R, Boedeker E, Friedrich U, et al. Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon. *Eur Respir J* **2011**; 39:669–76.
16. Horvath G, Andersson H, Nemes S. Cancer odor in the blood of ovarian cancer patients: a retrospective study of detection by dogs during treatment, 3 and 6 months afterward. *BMC cancer* **2013**; 13:396.
17. Bekoff M. Observations of scent-marking and discriminating self from others by a domestic dog (*Canis familiaris*): tales of displaced yellow snow. *Behav Processes* **2001**; 55:75–9.
18. Berthoud D. Investigating scent marking in dogs. *Vet Rec* **2006**; 158:572.
19. Asa CS, Mech LD, Seal US, Plotka ED. The influence of social and endocrine factors on urine-marking by captive wolves (*Canis lupus*). *Horm Behav* **1990**; 24:497–509.
20. Kang CI, Kim SH, Kim HB, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* **2003**; 37:745–51.
21. National Academy of Sciences. *Guide for the Care and Use of Laboratory Animals*. Washington, DC: National Academy Press; **1996**.
22. The prevention and management of urinary tract infections among people with spinal cord injuries. National Institute on Disability and Rehabilitation Research consensus statement. January 27–29, 1992. *SCI Nurs* **1993**; 10:49–61.
23. Bomers MK, van Agtmael MA, Luik H, et al. Using a dog's superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study. *BMJ* **2012**; 345:e7396.
24. Roine A, Veskimäe E, Tuokko A, et al. Detection of prostate cancer by an electronic nose: a proof of principle study. *J Urol* **2014**; 192:230–4.
25. Trincavelli M, Coradeschi S, Loatfi A, et al. Direct identification of bacteria in blood culture samples using an electronic nose. *IEEE Trans Biomed Eng* **2010**; 57:2884–90.