Can dogs smell prostate cancer?

BY STEPHANIE SMITH, ROB MILLS, COLIN COOPER AND DANIEL BREWER

For centuries we have known that man's best friend has an exceptional sense of smell. 'Sniffer' dogs are found in a wide range of roles, including drug and explosive detection as part of airport security, helping emergency services locate survivors during natural disasters, and even aiding biologists in tracking rare species in the wild. Detection dogs have also been used in numerous medical contexts, from the detection of COVID-19 through to Parkinson's disease [1,2]. The first documented case of canine-assisted detection of cancer appeared 35 years ago as a letter to the editor in *The Lancet*, describing the case of a Border Collie-Dobermann crossbreed who showed intense interest in her owner's mole that was later histologically confirmed to be a malignant melanoma [3]. More recently, formalised studies exploring the olfactory ability of dogs to detect prostate cancer have been reported in the literature [4].

Stephanie Smith's greyhound Lexi, a very good hospital therapy dog but not yet trained to sniff out cancer.

How does a dog's nose work?

When a dog sniffs, approximately 12% of each breath passes directly from the nostrils to the olfactory region via the upper flow pathway (with the remainder passing into the lower pathway, down to the pharynx and lungs) [5]. The olfactory epithelium, located in the nasal cavity, contains olfactory receptor cells which each express one type of olfactory receptor. Identification of odours and detection of their intensity involves activating unique combinations of olfactory receptors, which signal to the olfactory bulb where signals are modulated and filtered prior to onward transmission to the olfactory cortex. Dogs can have over 200 million olfactory receptors (as compared to only 50 million in humans) [6]. Interestingly, the volume of the dog's olfactory bulb is larger than humans despite dogs having smaller brains (human olfactory bulb 0.06 cm^3 vs. dog 0.18 cm^3) [7]. Unlike humans, dogs also have an additional apparatus called the vomeronasal organ (VNO or Jacobson's Organ) which is found just above the roof of their mouth and is thought to be involved in the detection of pheromones.

Of course, there are other species, such as African elephants, that possess even more advanced olfactory abilities than dogs; African elephants are believed to have the most sensitive sense of smell in the animal kingdom, with approximately 2000 olfactory receptor genes and the added advantage of their trunk. However, given their trainability and compact size, dogs are a far more practical choice as diagnostic assistants — especially when factoring in the door size of most urology outpatient clinics!

What does prostate cancer smell like?

Whilst it is unknown to us what prostate cancer truly smells like, dogs can detect volatile organic compounds (VOCs) through scent. As the name suggests, VOCs are organic compounds with a high vapour pressure at room temperature. These include acids, alcohols, ketones, aldehydes and amines [8], and are present in the urine [9]. The specific combination of VOCs in an individual's urine is unique and can reflect metabolic status and pathological changes [10], which can be influenced by (and therefore be a marker for) prostate cancer.

Key concepts in diagnostic modelling

A diagnostic model is a system or tool used to predict outcomes or classify patients based on inputs such as test results. In the context of detecting prostate cancer using canine olfaction, the diagnostic model refers to the trained dogs, which are taught to detect volatile organic compounds (VOCs) associated with prostate cancer in urine samples.

To build a diagnostic model, the first step is to collect data for both training and testing. In our example, the **training set** would consist of urine samples from two groups: patients with prostate cancer and patients without it. Ideally, the number of samples from both groups would be balanced to give the dog an equal chance to learn from both positive and negative cases. Training the dogs is done using **supervised learning**, where the dog is exposed to the urine samples and provided with the correct answer, indicating whether the sample is from a patient with prostate cancer or not. Dogs are rewarded (such as with food or play) when they correctly identify cancer-positive samples and are trained to ignore samples from cancer-negative individuals. Through repetition and reinforcement, the dog's ability to detect prostate cancer improves over time.

The testing set consists of a separate set of urine samples that the dogs have never encountered before – blind testing. This is used to assess how well the dog can generalise its learning and make accurate predictions in a real-world setting, without cues or guidance from handlers. The model's performance can be evaluated using sensitivity and specificity. In this example, the sensitivity measures how well the dog identifies cancer-positive samples and specificity measures how accurately the dog ignores control samples. A graphical representation of a diagnostic test performance across different threshold levels can be produced using the receiver operating characteristic (ROC) curve, which plots sensitivity against 1 – specificity (the false positive rate). The area under the curve (AUC) quantifies the ability of the test to distinguish between those with or without the condition of interest, ranging from 0.5 (no discrimination) up to 1.0 (perfect discrimination). In this example, a high AUC of above 0.9 would suggest the dogs are excellent at distinguishing between urine samples from prostate cancer and healthy controls.

One common challenge in diagnostic modelling is overfitting, which can occur if there is a characteristic of the training samples not generalisable to the population, or if the population as a whole was not adequately represented in the training samples. For example, in the context of canine olfaction if all the urine samples from prostate cancer patients in the training set were also patients with haematuria, and the dogs were detecting the scent of blood rather than VOCs associated with prostate cancer, then overfitting could occur. Alternatively, if all the samples in the training set were from patients with a specific characteristic (for example, the same ethnicity), the model may not be useable in other populations. The problem of overfitting is generally identified if the performance of the test set is poorer than the training set (e.g., if the AUC was 0.89 in training but 0.55 in the test set, you could conclude that the model was overfitted to the training data).

Variability between dogs is another challenge, as different dogs may perform differently based on factors like their breed, temperament or individual training. Consistency and quality of urine samples and clinical information are crucial for accurate model training. Finally, external factors such as environmental distractions may influence the dogs' performance, similar to the 'noise' in data that can impact machine learning outcomes.

How good are dogs at smelling prostate cancer?

Cornu et al. assessed the effectiveness of a trained Belgian Malinois in detecting prostate cancer by identifying urine samples from 33 prostate cancer patients and 33 healthy controls. The dog was trained using operant conditioning with a clicker over a period of 24 months [11]. Their results demonstrated both sensitivity and specificity for detection of cancer to be 91% in the test set.

Taverna et al. evaluated the ability of two three-year old female German Shepherd explosion detection dogs, Zoe and Liu, to identify prostate cancer-specific VOCs in a large number of urine samples [12]. Their study, published in the *Journal of Urology*, involved 362 prostate cancer patients and 540 healthy controls. Both dogs exhibited excellent sensitivity and specificity: with one dog reaching 100% sensitivity and 98.7% specificity, and the other demonstrating 98.6% sensitivity and 97.6% specificity.

In August 2024, Hermieu et al. unleashed the findings of their study, 'Contribution of canine olfaction in the diagnostic strategy of intermediate and high-risk prostate cancer: a double-blind validation study' in the *World Journal of Urology* [4]. They trained seven dogs to analyse urine samples for prostate cancer detection. Six of the dogs demonstrated a specificity of over 75% for detecting International Society of Urological Pathology Grade Group (ISUP GG) ≥ 2 disease. Notably, Phoebe the Malinois achieved a sensitivity of 86% and a specificity of 78%, outperforming MRI with Prostate Imaging–Reporting and Data System (PI-RADS) ≥4, which showed only 83% sensitivity and 41% specificity for detecting ISUP GG ≥ 2 disease in the same study.

Florin the Labrador and Midas the Wire-Haired Hungarian Vizsla were put to the test in a more complex study by Guest et al. who evaluated the feasibility of integrating canine olfaction with VOC analysis using gas chromatography-mass spectroscopy artificial neural network-assisted examination and microbial profiling [13]. They found that their canine olfaction system had a 71% sensitivity and 70–76% specificity for the detection of Gleason 9 prostate cancer.

The future: artificial noses

Whilst you may have seen dogs in your hospital (including the author's greyhound) providing emotional support to patients and staff via the Pets as Therapy charity, bringing them into the pathology laboratory or urology clinic for urine analysis poses several challenges. Obvious limitations with using dogs for cancer detection include concerns around scalability, reproducibility and standardisation as well as cost-effectiveness. But what if we could create an artificial nose capable of detecting prostate cancer from VOCs in urine samples? In addition to being more likely to successfully negotiate the complex world of diagnostic device legislation and accreditation requirements, perhaps this may be more likely to yield a model capable of distinguishing between any prostate cancer and clinically significant disease. With advancements in biosensing technologies, analytical methods as well as machine learning, the idea of such an artificial nose is not as far-fetched as it might initially seem.

Gao et al. analysed urinary VOCs using gas chromatography-mass spectrometry, developing a model for prostate cancer diagnosis which achieved an AUC of 0.86 in their test cohort (as compared to the prostate specific antigen (PSA)-based diagnosis model AUC of 0.54) [14]. Taverna et al. evaluated an electronic nose (eNose) equipped with metal oxide semiconductor sensors that interact with urinary VOCs to produce variation in electrical resistance [15]. In their prospective blinded study of 174 subjects (88 with prostate cancer, and 86 controls), the eNose was found to have an AUC of 0.82 (95% CI 0.76-0.88) for detection of any grade of prostate cancer.

Conclusion

For now, while Phoebe the Mallinois and her canine colleagues have demonstrated remarkable abilities in detecting prostate cancer through olfaction, we can rest assured they are not poised to replace urologists anytime soon. However, understanding the scientific basis of canine olfaction paves the way for exciting cross-disciplinary research, potentially leading to the development of artificial noses that could serve as non-invasive tools for early prostate cancer diagnosis and monitoring.

References

1. Ungar PJ, Pellin MA, Malone LA. A One Health perspective: COVID-sniffing dogs can be effective and efficient as public health guardians. *J Am Vet Med Assoc* 2024;**262(1)**:13–6.
2. Gao CQ, Wang SN, Wang MM, et al. Sensitivity of sniffer dogs for a diagnosis of Parkinson's Disease: a diagnostic accuracy study. *Mov Disord* 2022;**37(9)**:1807–16.
3. Williams H, Pembroke A. Sniffer dogs in the melanoma clinic? *The Lancet* 1989;**333(8640)**:734.
4. Hermieu JF, Hermieu M, Roux A, et al. Contribution of canine olfaction in the diagnostic strategy of intermediate and high-risk prostate cancer: a double-blind validation study. *World J Urol* 2024;**42(1)**:497.
5. Craven BA, Paterson EG, Settles GS. The fluid dynamics of canine olfaction: unique nasal airflow patterns as an explanation of macrosmia. *J R Soc Interface* 2010;**7(47)**:933–43.

6. Alvites R, Caine A, Cherubini GB, et al. The olfactory bulb in companion animals-anatomy, physiology, and clinical importance. *Brain Sci* 2023;**13(5)**:713.
7. Kavoi B, Hassanali J. Comparative morphometry of the olfactory bulb, tract and stria in the human, dog and goat. *Int Jour of Morp* 2011;**29**:939–46.
8. De Lacy Costello B. 'Volatile organic compounds (VOCs) found in urine and stool.' In: Amann A, Smith D (Ed.). *Volatile Biomarkers: Non-Invasive Diagnosis in Physiology and Medicine*. USA; Elsevier; 2013: p. 405–62.
9. Liu Q, Fan Y, Zeng S, et al. Volatile organic compounds for early detection of prostate cancer from urine. *Heliyon* 2023;**9(6)**:e16686.
10. Warli SM, Firsty NN, Velaro AJ, Tala ZZ. The olfaction ability of medical detection canine to detect prostate cancer from urine samples: progress captured in systematic review and meta-analysis. *World J Oncol* 2023;**14(5)**:358–70.
11. Cornu JN, Cancel-Tassin G, Ondet V, et al. Olfactory detection of prostate cancer by dogs sniffing urine: a step forward in early diagnosis. *Eur Urol* 2011;**59(2)**:197–201.
12. Taverna G, Tidu L, Grizzi F, et al. Olfactory system of highly trained dogs detects prostate cancer in urine samples. *J Urol* 2015;**193(4)**:1382–7.
13. Guest C, Harris R, Sfanos KS, et al. Feasibility of integrating canine olfaction with chemical and microbial profiling of urine to detect lethal prostate cancer. *PLoS One* 2021;**16(2)**:e0245530.
14. Gao Q, Su X, Annabi MH, et al. Application of urinary volatile organic compounds (VOCs) for the diagnosis of prostate cancer. *Clin Genitourin Cancer* 2019;**17(3)**:183–90.
15. Taverna G, Grizzi F, Tidu L, et al. Accuracy of a new electronic nose for prostate cancer diagnosis in urine samples. *Int J Urol* 2022;**29(8)**:890–6.

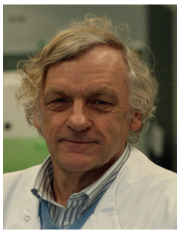
AUTHOR

Stephanie Smith,

NIHR Doctoral Research Fellow and Urology Registrar (ST6), Norfolk and Norwich University Hospital and University of East Anglia, UK.

Rob Mills,

Consultant Urological Surgeon, Norfolk and Norwich University Hospital, UK.



Colin Cooper,

Professor of Cancer Genetics. University of East Anglia, UK.

Daniel Brewer,

Professor of Medical Bioinformatics and Genomics, University of East Anglia, UK.

Declaration of competing interests: Stephanie Smith is funded by an NIHR Doctoral Research Fellowship (NIHR unique award identifier 303302). The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care. Patent applications have been filed by CSC and DSB for the use of the Prostate Urine Risk (PUR), DESNT and anaerobic bacteria biomarker set (ABBS) in prostate cancer diagnosis and prognosis.