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Trained dogs can detect the odor of hemangiosarcoma in canine blood samples

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ABSTRACT

Hemangiosarcoma (HSA) is a common, aggressive, and deadly vascular cancer in dogs that is usually diagnosed only at advanced stages. Because treatment options are limited once HSA is advanced, early detection is essential to improving survival and quality of life. Five trained bio-detection dogs were evaluated using double-blinded tests with automated olfactometer line-ups containing blood serum samples from dogs with confirmed HSA, non-cancerous diseases other than HSA (diseased controls), and healthy controls. All test samples were novel to the dogs. Across all 423 blinded trials, accuracy was 70.0 % (range = 57.1–78.6 %). First-trial accuracy, representing each dog's initial response to a novel matched sample set, averaged 70.0 % (range = 58.3–83.3 %). When considering each dog's first encounter with each sample, dogs achieved an overall sensitivity of 70.0 % and specificity of 70.0 %. A mixed-effects logistic regression showed that dogs alerted to HSA samples in 73.4 % of presentations, compared with 21.3 % of diseased controls and 17.1 % of healthy controls. Dogs were over 10 times more likely to alert to HSA than to diseased controls (OR = 10.2, $p < .001$) and over 13 times more likely than to healthy controls (OR = 13.3, $p < .001$). This study finds that trained dogs can distinguish serum samples from dogs with HSA from those of healthy and diseased controls, indicating that HSA produces a detectable odor signature. Conclusions are constrained by the limited number of HSA samples. These results suggest a potential feasibility of VOC-based detection for canine HSA.

Introduction

Cancer represents one of the most significant health challenges for companion animals, with lifetime cancer risk in dogs estimated between one in two and one in three (Ritt, 2023). Among the many tumor types affecting dogs, hemangiosarcoma (HSA) is particularly devastating. HSA is an aggressive, malignant neoplasm of vascular endothelial origin that predominantly affects middle-aged to older dogs, with breed predispositions reported for German Shepherds, Golden Retrievers, and Labrador Retrievers (Schultheiss, 2004; Vail et al., 2020). It accounts for 45–51 % of canine splenic malignancies and approximately 2–7 % of all canine tumors (Smith, 2003; Vail et al., 2020). Considering the size of the U.S. dog population, this translates to an estimated 0.5–2.5 million dogs expected to develop HSA over their lifetime, underscoring its significance as a major canine health problem (Ritt, 2023).

Canine HSA has been described as a "silent killer" because it is often not diagnosed until a seemingly healthy dog suffers an acute collapse due to a ruptured tumor. This places a heavy burden on emergency and critical care teams, as many patients present in shock or with hemoabdomen requiring urgent stabilization. HSA can arise in any organ or tissue containing vascular structures; however, visceral forms of HSA are more common than cutaneous forms and are associated with a poorer prognosis (Schultheiss, 2004). Because clinical signs often do not appear until the disease has progressed, the development of early diagnostic methods would be hugely valuable, allowing treatment to begin before cancer has advanced to critical stages. Prognosis is currently poor, with median survival times of only 2–3 months following splenectomy, and 4.5–9.1 months when surgery is combined with chemotherapy, depending on disease stage (Vail et al., 2020). Despite its prevalence and lethality, there are no early diagnostic tools for HSA, and diagnosis is currently reliant on histopathology following invasive sampling. Earlier detection could allow more timely intervention and significantly

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improve clinical outcomes.

In human medicine, distinctive patterns of volatile organic compounds (VOCs) have been identified in a wide range of diseases, including several cancers, using both analytical profiling methods and canine olfaction (Drabińska et al., 2021; Lippi & Heaney, 2020). These VOC patterns are thought to be by-products of altered cellular metabolism and oxidative stress, which are released into biofluids and exhaled breath (Waltman et al., 2020). They are present in concentrations ranging from parts-per-million in blood to parts-per-trillion in breath (Schmidt & Podmore, 2015). Dogs, with their extraordinary olfactory acuity, can detect odorants at these low concentrations and synthesize complex VOC mixtures into disease-specific odor profiles (Angle et al., 2016; Walker et al., 2006). Unlike analytical devices, which may be confounded by background VOCs, dogs are able to integrate multiple cues and have been demonstrated to reliably categorize samples as disease-positive or disease-negative (Edwards et al., 2017), and differentiate between diseases that may have similar clinical presentations (Juge et al., 2022). This ability has been illustrated by studies showing that trained dogs can detect human cancers, such as prostate cancer, with sensitivities and specificities exceeding 90 %, performance that rivals or even surpasses conventional diagnostic methods, which can miss up to a quarter of true cases (Cornu et al., 2011; Roehl et al., 2002). Together, these findings underscore the remarkable diagnostic potential of canine olfaction and demonstrate that biological detection systems can achieve levels of precision and adaptability that remain challenging for current analytical technologies.

Research into olfactory detection of disease has historically centered on human health, where dogs have repeatedly demonstrated an ability to identify cancer-associated odor profiles with high sensitivity and specificity (Juge et al., 2022). More recently, this frontier has begun to extend into veterinary medicine, with growing interest in whether canine olfaction can be applied to detecting cancers in other dogs. Malone et al. (2023) demonstrated that trained dogs could differentiate saliva samples from cancer-affected and negative-control healthy dogs with 98 % specificity and 90 % sensitivity; however, this study did not include samples from dogs with noncancerous diseases as controls, leaving open the possibility that dogs learned to recognize general disease or inflammation rather than cancer-specific odors. More recently, Desmas-Bazelle et al. (2024) showed that dogs could detect urothelial carcinoma from urine samples, even when challenged with both negative control healthy samples and those from dogs with benign urinary tract disease. These early studies are both novel and promising, illustrating that detection dogs can recognize malignant processes in other dogs. Nevertheless, expanding canine olfaction to aid in canine health concerns remains in its infancy, and further work is required to define disease-specific odor profiles that can ultimately inform the development of diagnostic tools.

To our knowledge, no studies to date have investigated canine blood serum as a biological medium to test bio-detection dogs, despite its central role in systemic physiology and disease processes. Further, no work has focused on canine HSA as the disease of interest. This gap is particularly striking because HSA is one of the most significant cancers in dogs, and a disease that veterinarians, owners, and breeders consistently cite as a pressing concern. As such, this study provides proof-of-concept information both on the potential use of canine serum as a substrate for this type of VOC-based research and information on the detectability of canine HSA. The present study design addresses limitations of previous studies in this field by including a diseased control group with noncancerous illnesses to test whether dogs can discriminate hemangiosarcoma (HSA) from other disease states. Further, the use of automated olfactometers, randomized double-blind trial presentation, and mixed-effects logistic modeling represent methodological advances that reduce bias and strengthen inference relative to earlier designs.

The objective of this study was to determine whether trained dogs could discriminate between blood serum samples from dogs with HSA, those with other noncancerous illnesses (diseased), and healthy negative controls. By establishing proof-of-concept that HSA is associated with a detectable VOC profile in serum, this study represents a critical first step toward minimally invasive diagnostic tools. While trained dogs are unlikely to represent a practical end-point diagnostic tool due to scalability and logistical limitations, they can provide robust biological evidence for the existence of a VOC profile that can subsequently be characterized and translated into deployable technologies. Establishing a biological signal provides the foundation for chemical and engineering efforts to identify the constituent compounds and develop scalable diagnostic tools. Such tools could be implemented in routine screening for at-risk dogs, support earlier intervention, and improve prognosis. Beyond veterinary medicine, this research also informs broader biomarker discovery efforts, providing translational insights relevant to analytical chemistry, sensor engineering, and the development of electronic nose technologies.

Materials and methods

Animals

All training and testing procedures complied with ARRIVE guidelines. Procedures utilizing PVWDC-owned dogs were conducted under approval from the Institutional Animal Care and Use Committee (IACUC number 807741) and procedures with privately owned dogs were conducted with informed consent under an approved Personally Owned Animals Protocol (POAP number 807129). Seven dogs began participation in this study, of which five dogs reached testing criteria. Demographic details of these dogs are described in Table 1. The handlers of the privately owned dogs (n = 4) provided informed consent prior to their dog's involvement in this study.

Samples

Blood serum samples from HSA-positive and HSA-negative dogs (both healthy and with noncancerous diseases) were procured by Morris Animal Foundation's Golden Retriever Lifetime Study (GRLS), Ryan Veterinary Hospital of the University of Pennsylvania (VHUP), Tufts University (Tufts), and Colorado State University (CSU). Blood samples

Table 1
Demographic details of the seven detection dogs trained at the Penn Vet Working Dog Center (PVWDC, Philadelphia, Pennsylvania, USA) to detect blood serum samples from dogs with hemangiosarcoma (HSA). Each dog's name, sex, age (y), reproductive status, breed, prior detection odor experience, and ownership are provided.

Dog name	Sex[a]	Age (y)	Reproductive status	Breed	Odors learned prior to this study[b]	Owner
Dog1	F	11	Spayed	Mix	UDC, CWD	Privately owned
Dog2	M	3	Intact	Belgian Malinois	UDC, PTSD	Privately owned
Dog3	M	5	Neutered	Labrador Retriever	UDC, CWD	PVWDC
Dog4	F	7	Spayed	Smooth Collie	UDC, CWD, pancreatic cancer	Privately owned
Dog5	F	11	Spayed	German Shepherd	UDC, CWD, ovarian cancer	PVWDC
Dog6	F	4	Spayed	Hound mix	UDC, CWD	Privately owned
Dog7	F	4	Spayed	Labrador Retriever	UDC, CWD	PVWDC

[a] F = female, M = male
[b] UDC = Universal Detection Calibrant, CWD = chronic wasting disease, PTSD = post-traumatic stress disorder

procured at VHUP were conducted under the approval of the Personally Owned Animals Protocol (POAP number 807536). Samples were collected during veterinary examinations and were confirmed to have splenic, cardiac, visceral, or non-specified HSA via histopathology, either on biopsies from live patients or necropsies. GRLS samples were all procured from Golden Retrievers, while samples from VHUP, Tufts, and CSU included a variety of dog breeds. Each collection site provided matched triads of samples consisting of one HSA, one diseased control, and one healthy control, all age- and sex-matched within site. This design prevented any site-related odor or storage factors from aligning with diagnostic category.

Diseased control samples consisted of serum from dogs with non-neoplastic conditions such as inflammatory, endocrine, gastrointestinal, or benign organ diseases, confirmed through clinical or pathological diagnosis. Diseased controls were selected primarily to match the age and sex of the dogs with HSA and secondarily to represent a broad range of non-cancerous but commonly encountered illnesses. Healthy control dogs were confirmed to be clinically healthy at their most recent veterinary examination. Comprehensive details on each case used at test are provided in Supplementary Table 1.

Test sets were selected using a random number generator from the total list of sample sets (n = 158 sets; 108 GRLS, 33 VHUP, 9 CSU, 8 Tufts), with each set containing an HSA-positive, diseased-negative, and healthy-negative sample which were matched for age and sex. Although most samples were obtained through the GRLS, this biobank includes dogs enrolled across multiple veterinary clinics throughout the United States. While uniform long-term storage could contribute to some shared background odor, GRLS samples were evenly distributed in matched triads across disease categories (HSA, healthy, diseased), controlling for potential site bias. Serum samples were stored at −80 C until use and went through a maximum of two freeze-thaw cycles. Training samples were shown a maximum of three times per dog, with samples previously encountered by a dog being described as “familiar” to them and samples never encountered before being described as “novel”. Samples (100ul) were presented using the automated olfactometer system described by Aviles-Rosa et al. (2021). Three olfactometers were arranged in a lineup and sample locations were pseudorandomized by the olfactometer software system (Fig. 1).

Training

Prior to this study, dogs were taught mechanics on how to search and alert on the olfactometers using Universal Detection Calibrant (UDC) as a training odor (Furton & Beltz, 2017). Dogs were trained to perform a final alert by holding their nose within the olfactometer port for several consecutive seconds (Supplementary Video 1). Dogs were also trained to perform a consistent “blank behavior” to indicate the target odor was not present by searching each olfactometer and either coming to a low table outside of the search area or laying down within the search area (Supplementary Video 2).

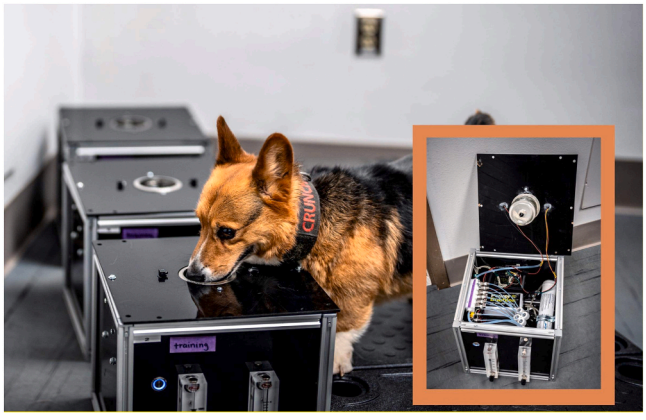

Fig. 1. An image of the olfactometer line-up. Embedded image shows the inner workings of the olfactometer.

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Dogs were trained using positive reinforcement with food rewards delivered contingent on correct responses. A correct response was defined as either a correct alert to a target (HSA) sample or a correct “blank” behavior when no target was present. Rewards were withheld following incorrect responses. Food rewards varied according to individual dog preference and owner input, and included Charlee Bear® Dog Treats (Gott Pet Products, St. Francis, WI, USA), Pupford® Beef Jerky Treats (Pupford LLC, Salt Lake City, UT, USA) and Purina® Pro Plan® Veterinary Diets OM Overweight Management kibble (Nestlé Purina PetCare Company, St. Louis, MO, USA). Dogs were not food deprived for training or testing. All dogs were provided with water *ad libitum*. Each dog completed two training sessions per week, each lasting approximately 10–30 min. Training sessions typically comprised 7–20 trials. All sessions were conducted under the supervision of experimenter CW. For Dog2, Dog3, Dog5 and Dog7, CW served as both handler and experimenter. For Dog1, Dog4, and Dog6, the dog’s owners acted as handlers and delivered food rewards, while CW was the experimenter, overseeing each session, managing the olfactometers and providing real-time feedback to ensure consistency in procedure. Initial training sessions were conducted unblinded, meaning that the handler and experimenter knew the location of the HSA sample within the lineup.

Dogs were trained to differentiate serum samples of HSA-positive and control (diseased and healthy) dogs. When first learning the odor, dogs were first presented with an HSA-positive sample in one olfactometer alongside two olfactometers presenting the air from empty vials. This provided the dogs with errorless learning as the target odor was the only odor present within the lineup. After being positively reinforced for alerting on the target odor several times, control odors (serum samples from diseased and healthy dogs) were introduced. Dogs were rewarded for checking and passing distractor samples and holding their nose in the olfactometer presenting the HSA sample for several seconds. Dogs were allowed to perform a free search pattern, meaning that dogs could search the olfactometers in any order and could continue searching until they performed a correct final response. However, only the dogs’ first decision (e.g., the sample that they performed their trained final response on, or calling a “blank”) was considered when calculating accuracy during training. One dog (Dog3) did not show sufficient engagement during the initial training phase and was withdrawn from the study.

Across this training phase, dogs were presented with novel (mean = 60, min = 43, max = 73) and familiar (mean = 13, min = 7, max = 18) matched sample sets from the four locations (GRLS, VHUP, Tufts, and CSU). The HSA samples included in the training sets were splenic (n = 53), cardiac (n = 15), visceral (n = 19), and non-specified (n = 3). Each dog saw between 14–24 unique matched sets with splenic HSA, 7–12 matched sets with cardiac HSA, and 12–15 matched sets with visceral HSA. Thus, while all three HSA types were represented, training exposure was not balanced across types, but was proportionate to what would be presented at test. Across training sessions, additional criteria were gradually introduced to approximate the final test conditions. These progressive changes included using full matched sets from the first trial onward, concealing the target sample’s position from both handler and experimenter, and transitioning toward the seven-trial test format.

To qualify for testing, dogs were required to achieve an accuracy of at least 4 correct first trials out of 6 sessions under test-criteria. A dog’s initial response was defined as its performance on the first trial of each session. Specifically, this was the sample the dog selected when first presented with a novel lineup containing one matched HSA, one healthy, and one diseased sample. An initial response was considered correct if the dog performed its trained final response (alert) on the target odor and withheld an alert from the two control samples,

demonstrating recognition of HSA on first presentation of a novel set. If a dog "false alerted" (i.e., alerted on a control sample) or performed a blank behavior when a target sample was present, the initial response was scored as incorrect. Dogs continued to be presented with novel sample sets until they met the testing criterion. A second dog (Dog5) was removed during qualification due to rapidly progressing age-related health concerns.

Testing

In detection-dog studies, *double-blind* refers to testing conditions where neither the handler nor any person in the testing room is aware of the target's presence or location during a trial (Organization of Scientific Area Committees for Forensic Science, Dogs & Sensors Subcommittee, 2024). The olfactometer software concealed this information from all personnel, ensuring blinding at both handler and experimenter levels. This system meant that the computer screen did not display information about the trial, so the dog handler and experimenters present in the testing space did not know whether it was a "hot" trial (e.g., HSA is present in the line-up), or "blank" trial (e.g., no target present, only control samples). Further, in "hot" trials, neither the dog handler nor experimenters knew the location of the HSA sample (Olfactometer 1, 2 or 3) as the system concealed this information. The dogs' first choice per trial was considered in the analysis (e.g., the first sample that they performed their trained final response on, or calling a "blank").

Dogs were presented with 12 matched sets of novel test samples (10 from GRLS, 2 from VHUP), with each set presented in its own testing session. On average, dogs took part in two testing sessions per week. Test sets contained splenic (n = 7), cardiac (n = 3), and visceral (n = 2) HSA samples (Supplementary Table 1). Along with a novel HSA-positive sample, each set contained an age- and sex-matched novel diseased sample and healthy sample. Control proportions were randomized such that dogs were presented either with one of each control sample, or two of the same control sample within a trial. Each test session consisted of seven trials, with a minimum of one blank trial per session. The placement of blank trials was pseudo-randomly allocated by the computer, as the first trial was never a blank trial. If a dog had not encountered a blank trial by trial seven, an additional trial was run to ensure that each test session included at least one blank trial.

Unblinded training sessions were interspersed between test sessions to avoid compounding effects of continuous double-blind trials. During these training sessions, dogs saw a mix of novel (mean = 4, min = 1, max = 9) and familiar samples (mean = 8, min = 7, max = 10) to avoid a large discrepancy between test and training sessions. These between-test training sessions were presented on the same day as test sessions, either before or after, with an interim break period between test and training sessions during which time the dogs left the testing space. Results from these training sessions were not included in the test analyses.

Olfactometer data collection

Data on dogs' performance were collected via infrared (IR) sensors embedded in the olfactometers, which recorded the duration of time each dog held its nose in a given sample port. Accuracy was calculated by comparing the location of the target sample, as determined by the olfactometer code (Olfactometer 1, 2, or 3, or "blank" if no target was present), with the dog's first decision in each line-up. The alert time, the duration a dog was required to maintain its nose within an IR beam to trigger a final response, was set between 2.0- and 3.5-seconds during testing. For "hot" trials (target present), a trial was scored as correct if the dog maintained the alert time at the olfactometer presenting the HSA sample. Trials were marked incorrect if the dog held the alert time at a control sample or failed to perform a trained final response after checking all three olfactometers. For "blank" trials (no target present), a trial was scored as correct if the dog briefly investigated each port (breaking each IR beam for less than the alert threshold) and then refrained from triggering any beam for an additional 7 s, indicating an "all-clear" response. If a dog performed its trained final response on any olfactometer during a blank trial, the trial was marked incorrect.

Statistical analyses

A test *trial* represented a single instance of the dog being released by the handler to make a discrimination choice across the three-olfactometer line-up. A test *session* was defined as each grouping of 7–8 test trials conducted on a matched set of three samples (one HSA, one diseased, and one healthy control). Within each test session, the same three samples were used throughout, with their presentation order randomized by the olfactometer trial-control code.

Accuracy was summarized descriptively for all test trials within a session, and separately for first-trial (initials) data, representing the dog's first exposure to each new sample set before any feedback was given. These first-trial accuracy values provided an indication of the dog's unreinforced category knowledge and are presented as part of the descriptive statistics. False positives were further divided into those occurring on healthy controls versus non-HSA diseased controls, and false negatives were attributed to specific HSA-positive samples.

Sensitivity and specificity were calculated at the sample-level, classifying each dog's first committed response to each novel test sample (n = 12 HSA, n = 12 diseased control, n = 12 healthy control) as TP, FN, TN, or FP. An alert to an HSA sample on first encounter was classified as a TP. An alert to a control sample was classified as a FP, even if the dog subsequently alerted correctly to the HSA within the same trial. A sniff-and-pass (no alert) on a control sample was classified as a TN. A sniff-and-pass on an HSA sample was classified as a false negative (FN) only if the dog later alerted on a control sample within that same trial (i.e., made an incorrect choice). This analysis used infrared (IR) beam data and nose-poke order recorded by the olfactometers (see Supplementary Data File 1) to determine which samples the dogs physically investigated, in what order, and how they responded on first encounter.

Model 1: overall alerting performance across all trials

The primary aim of this study was to determine whether trained dogs could reliably detect blood serum samples from dogs with HSA. This model included all test trials. A binomial generalized mixed-effects model was used with Alert outcome (1 = dog alerted to the sample, 0 = did not alert) as the dependent variable at the sample level. Sample type (HSA, diseased control, healthy control) was included as a fixed effect. Dog and Set ID were included as random intercepts to account for repeated measures within dogs and across matched sample sets. Model-based marginal probabilities with 95 % Wald confidence intervals were reported. Direct comparisons between sample types were obtained using two-class intercept-only mixed-effects logistic models with the same random-effects structure; odds ratios (OR), Wald z statistics, and two-sided p values ($\alpha = 0.05$) are presented.

Model 2: first-trial (initial) performance

Because each session represented a novel matched sample set, the first trial of each session ("initial") was analyzed separately to assess unreinforced detection performance prior to feedback (reward tone and treat for a correct HSA alert or no tone for an incorrect response). A binomial generalized mixed-effects model was used with Alert outcome (1 = dog alerted to the sample, 0 = did not alert) as the dependent variable at the sample level. Sample type (HSA, diseased control, healthy control) was included as a fixed effect, and Dog as a random intercept. Set ID was initially included as a random effect but was removed due to singular fits arising from the limited number of observations per set. Comparison of models with and without Set ID confirmed that fixed-effect estimates and standard errors were consistent, supporting that its exclusion did not bias the results. This model provided an estimate of the dog's conceptual recognition of the HSA odor prior to any feedback on those specific samples. Model-based

probabilities with 95 % Wald intervals were estimated for HSA, diseased, and healthy alerts (alerted trials only), and pairwise two-class mixed-effects logistic models were used to obtain OR, Wald z, and two-sided p values.

Model 3: detection consistency across HSA subtypes

To assess whether detection accuracy varied across cancer subtypes, a trial-level binomial generalized mixed-effects model was used with Trial accuracy (1 = dog correctly identified the cancer sample, 0 = incorrect or no alert) as the dependent variable. HSA subtype (splenic, cardiac, or visceral) was included as a fixed effect, with target port, distractor composition, trial index, and session index included as covariates. Dog and Set ID were included as random intercepts to account for repeated measures within dogs and heterogeneity across sample sets.

Of the 12 HSA-positive samples included in testing, 10 were obtained from GRLS and 2 from VHUP. Due to the small number of VHUP samples, source location was not modelled statistically, but descriptive summaries are presented.

All analyses were conducted in R (version 2023.12.0 +369) (R Core Team, 2023). Mixed-effects logistic regression models were fitted using the *lme4* package (Bates et al., 2015), with estimated marginal means and model diagnostics obtained via *emmeans* (Lenth, 2023) and *performance* (Lüdecke et al., 2021).

Results

Accuracy across first-trial-only and all trials

First-trial accuracy (n = 60 blinded test trials), representing each dog's initial response to a novel matched sample set before any feedback, averaged 70.0 % (42/60 trials correct) (range = 58.3–83.3 %). Across all 423 blinded test trials, dogs achieved an overall accuracy of 70.0 % (296/423 trials correct) (range = 57.1–78.6 %) (Table 2).

Sensitivity and specificity

Sample-level sensitivity and specificity evaluated each dog's first encounter with every individual novel sample (n = 60 HSA, n = 60 healthy, n = 60 diseased). Dogs achieved a mean sensitivity of 70.0 % (range = 53.3–83.3 %) and specificity of 70.0 % (range = 58.3–87.5 %) (Table 3). First encounter false positives were distributed as n = 14 on healthy controls and n = 22 on diseased controls.

While individual dogs varied in their sensitivity and specificity, all dogs showed discrimination between HSA and control samples. However, one particular HSA sample (R2: part of GRLS matched Set 107) showed markedly reduced detection accuracy and contributed disproportionately to false negatives, warranting separate consideration. Across all 36 repeated presentations of sample R2 where dogs were rewarded if they performed a trained final response to this sample, we found an accuracy of only 38.9 %. In comparison, accuracy in alerting to the other tested HSA samples ranged from 55.5 % to 91.4 % (for accuracy on each of the 12 HSA samples presented in test, see Supplementary Table 2).

Table 2
Accuracy and first-trial performance of each dog during test sessions. Mean total accuracy represents the average proportion of correct responses across all trials. Initial accuracy represents the proportion of test sessions in which the dog's first trial response was correct.

Dog	First Trial Correct	Total First Trials	First-Trial Accuracy (%)	Total Correct Trials	Total Trials	Mean Total Accuracy (%)
Dog1	9	12	75.0	58	86	67.4
Dog2	10	12	83.3	62	84	73.8
Dog4	9	12	75.0	66	84	78.6
Dog6	7	12	58.3	48	84	57.1
Dog7	7	12	58.3	62	85	72.9
Total	42	60	70.0	296	423	70.0

Table 3
Each dog's sensitivity and specificity on first encounter with each sample.

Dog	TP	FN	TN	FP	Sensitivity (%)	Specificity (%)
Dog1	9	3	13	11	75.0	54.2
Dog2	10	2	21	3	83.3	87.5
Dog4	9	3	19	5	75.0	79.2
Dog6	7	5	14	10	58.3	58.3
Dog7	7	5	17	7	58.3	70.8
Total	42	18	84	36	70.0	70.0

Given the poor performance on sample R2, we followed up with the sample provider to review the patient's diagnostic history. Pathology records revealed that the initial commercial laboratory report described splenic hemorrhage but did not confirm a tumor. A second review by Colorado State University (CSU) pathologists diagnosed the sample as HSA with concurrent hemorrhage, providing its classification as HSA. As such, it was delivered to our study as an HSA confirmed sample. However, during the study period, a third pathologist at CSU reviewed the sample and classified it as multifocal thrombosis leading to infarct and hematoma, rather than HSA. Because of these conflicting reads, the case has been sent for consensus review among all three pathologists. The sample remains currently under adjudication, with the likelihood that the HSA classification will be overturned. Because a final pathology determination for this sample remains pending, we have retained it in the dataset for transparency. All analyses were rerun with and without this case to provide the most complete information possible. When considering accuracy, sensitivity and specificity, if the session where the sample set containing R2 were excluded, the mean accuracy becomes 72.6 % (range = 62.3–81.8 %), mean sensitivity is 72.7 % and mean specificity is 71.8 %.

While the number of samples from each location were too small to carry out hypothesis testing, descriptive statistics are presented to confirm that dogs were able to detect and an HSA odor in breeds beyond only Golden Retrievers (as all samples provided by GRLS were from Golden Retrievers). Across 353 trials using GRLS matched sets, accuracy was 71.4 %. For the 70 trials using VHUP matched sets (including samples from Labrador Retrievers, Dutch Shepherd and a Mixed Breed dog), accuracy was 62.9 %. While the VHUP results appear modestly lower, performance remained within the same general range as GRLS, supporting the conclusion that the HSA odor signature is not specific to Golden Retrievers (breed information on VHUP samples provided in Supplementary Table 1).

Model 1: overall alerting performance across all trials

Dogs were significantly more likely to alert to HSA samples (probability = 0.73, 95 % CI [0.69, 0.78]) than to diseased controls (0.21, 95 % CI [0.17, 0.26]) or healthy controls (0.17, 95 % CI [0.14, 0.21]) (Fig. 2). Pairwise contrasts indicated that dogs were 10 times more likely to alert to an HSA sample than a diseased control sample (OR = 10.2, z = 12.89, $p < .001$) and 13 times more likely to alert to an HSA sample than to a healthy control sample (OR = 13.3, z = 14.34, $p < .001$). Alerts to diseased and healthy controls did not differ significantly (OR = 1.3, z = 1.40, p = .34).

To evaluate the influence of the ambiguous sample R2 (GRLS Set 107), the model was rerun with all associated trials removed. Excluding this set resulted in only minor changes in estimated alert probabilities (HSA = 0.74, 95 % CI [0.66, 0.80]; diseased = 0.16, 95 % CI [0.12, 0.20]; healthy = 0.10, 95 % CI [0.06, 0.17]), confirming that the overall conclusions remain unchanged.

Model 2: first-trial (initial) performance

Restricting to the first trial of each session (n = 60), first alerts were

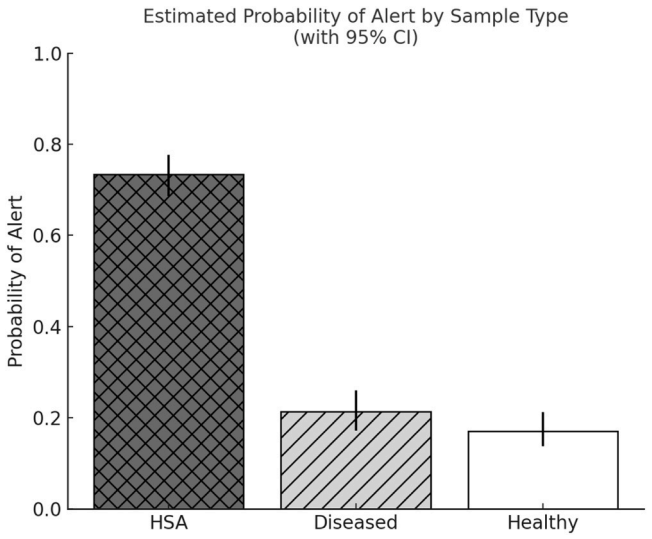

Fig. 2. Estimated probability of alerting to each sample type. Bars represent model-based probabilities of alert, with error bars showing 95 % confidence intervals. Results are derived from a binomial mixed-effects model with Dog and Set ID included as random effects.

to HSA in 42/60 (70 %), diseased controls in 11/60 (18 %), and healthy controls in 7/60 (12 %). Model-based estimates indicated a higher probability of alerting to HSA (0.70, 95 % CI [0.57, 0.80]) than to diseased (0.18, 95 % CI [0.10, 0.30]) or healthy samples (0.12, 95 % CI [0.06, 0.23]). Pairwise mixed-effects logistic models (random intercept for Dog ID) showed greater odds for HSA versus diseased (OR = 3.8, $z = 3.96$, $p < 0.001$) and HSA versus healthy (OR = 6.0, $z = 4.39$, $p < 0.001$), with no difference between diseased and healthy controls (OR = 1.6, $z = 0.94$, $p = 0.35$).

The first-trial model was rerun with all trials associated with sample R2 (GRLS Set 107) removed. Estimated alert probabilities were 0.73 (95 % CI [0.60, 0.83]) for HSA, 0.16 (95 % CI [0.09, 0.29]) for diseased controls, and 0.11 (95 % CI [0.05, 0.22]) for healthy controls. Overall conclusions were unchanged.

Model 3: detection consistency across HSA subtypes

In the trial-level sensitivity model considering all trials where HSA was present in the line-up, estimated detection probabilities were 69.7 % for splenic HSA, 85.5 % for cardiac HSA, and 76.9 % for visceral HSA. Although the odds ratio for cardiac relative to splenic was greater than 2 (OR = 2.56), this difference did not reach statistical significance ($p = .06$). Raw miss rates based on true positive and false negative counts were 15.3 % for cardiac, 31.6 % for splenic, and 25.0 % for visceral (Table 4). These findings should be interpreted with caution given the smaller number of cardiac and visceral presentations (85 and 60, respectively) relative to splenic (212). Our aim was not to establish definitive subtype differences, but rather to ensure that dogs were not responding exclusively to one subtype of HSA.

When ambiguous splenic sample R2 was excluded from analysis, splenic detection (miss rate = 31.6 %) improved modestly (miss rate = 27.1 %, TP = 132, FN = 49, n = 181). The overall model conclusions were unchanged.

Table 4
The number of true positives, false negatives and miss rates for each HSA subtype across all trials with HSA included in the line-up at test.

HSA Type	True Positives (TP)	False Negatives (FN)	Miss Rate (%)
Cardiac	72	13	15.3 %
Splenic	145	67	31.6 %
Visceral	45	15	25.0 %

Discussion

This study provides the first controlled preliminary evidence that trained detection dogs can discriminate blood serum samples from dogs with HSA from those of non-cancerous and healthy controls, indicating that HSA produces a distinct odor signature. Across 423 blinded test trials, dogs achieved an overall accuracy of 70.0 % and sensitivity and specificity both at 70.0 %. If the ambiguous sample R2 was omitted, accuracy, sensitivity, and specificity increased respectively to 72.6 %, 72.7 %, and 71.8 %. Mixed-effects models showed that dogs were significantly more likely to alert to an HSA sample than to diseased or healthy controls, both on first exposure and across repeated trials. These findings suggest that HSA produces a detectable odor signature and extends earlier work in veterinary oncology by moving beyond anecdotal reports and pilot studies into controlled, double-blinded testing.

Our results across all test trials (Model 1) align with, and expand upon, the two prior controlled studies assessing dogs detecting canine cancer through olfaction. Malone et al. (2023) reported that dogs distinguished saliva samples from cancer-affected and healthy dogs with a mean sensitivity of 90 % and specificity of 98 %. However, mixed-effects models were not reported and the absence of diseased controls in that study left unresolved whether dogs were detecting cancer-specific odor profiles or a more general "sickness odor." By including both healthy and diseased controls, our study addressed this concern and showed that detection was not driven solely by generalized illness. Desmas-Bazelle et al. (2024) trained dogs to detect urothelial carcinoma in urine and did include a diseased control group, dogs with non-malignant urinary tract disease. Desmas-Bazelle et al. (2024) reported an overall mean sensitivity of 80 % and specificity of 91.7 %. However, when restricted to unique donor samples to ensure that no samples were repeated between training and testing, performance dropped to 66.7 % sensitivity and 87.5 % specificity. It is important to consider the novelty of samples used in testing as previous studies have shown that dogs are highly skilled in memorizing biological samples, and that repeating samples from training to test may reflect memorization, rather than an understanding of the category which can be applied to novel samples (Elliker et al., 2014; Juge et al., 2022). Our study found a comparable sensitivity across sample sets that had never previously been shown to the dogs (70.0 % sensitivity in the current study, 66.7 % in Desmas-Bazelle et al., 2024), but with lower specificity (70 % in the current study, 87.5 % in Desmas-Bazelle et al., 2024) This suggests that dogs were slightly more likely to correctly identify the cancer sample, but were more prone to also making false alerts on control samples than the dogs in Desmas-Bazelle et al. (2024). These differences may be attributable to variation in testing paradigms (e.g., the olfactometer system used in the current study which uses air sampling the headspace of each vial versus the passive sample presentation used in previous studies), the volume of sample presented to the dog, prior training history, or biological differences in the VOC patterns associated with urothelial carcinoma versus HSA.

We compared two levels of performance: overall accuracy across all trials and accuracy on first trials only. This distinction is infrequently made in scent-detection research but is crucial to understanding the extent of dogs' learned odor recognition before feedback is provided. Once a dog has been rewarded for alerting correctly in an early trial, subsequent trials within that same session may begin to measure discrimination, how well the dog can tell the samples apart, rather than conceptual understanding of the disease category itself. Across-session learning can therefore inflate accuracy scores if dogs use reinforcement feedback to refine their choices over repeated exposures. While a small number studies, such as Desmas-Bazelle et al. (2024) have reported both cumulative and first-presentation results, and other studies have provided first-presentation results only (e.g., Crawford et al., 2022; Mallikarjun et al., 2024), most canine scent-detection papers summarize only cumulative accuracy across multiple exposures. In this study, first-trial accuracy (70.0 %) closely mirrored total accuracy (70.0 %),

suggesting that the dogs were not simply following feedback but had generalized understanding of the target odor even on their first exposure to a novel sample set. The parallel between Model 1 (all test trials) and Model 2 (first-trials only) indicates that the odor recognition achieved in this study likely reflects true conceptual learning rather than session-level shaping. Explicitly reporting first-trial data, as done here, should be adopted more widely in future canine detection studies, as incorporating first-trial analyses can reveal whether dogs are relying on genuine odor generalization or gradual reinforcement-driven discrimination. Moreover, exploring individual variation in these patterns may prove informative: some dogs in our study (Dog1, Dog2) showed higher performance on their initial trials than across multiple repetitions, possibly reflecting cognitive fatigue or reduced motivation over the session, whereas Dog7 showed the opposite pattern, improving across repeated trials after initially lower first-trial accuracy (see Table 2). Understanding these individual learning profiles could help optimize training protocols and may also explain why dogs remain a powerful, if variable, proof-of-concept model for olfactory biosensing, whereas engineered sensors may ultimately provide more stable, repeatable performance.

The range of diseased controls used in this study was broad and clinically relevant, helping to confirm that dogs were not simply differentiating "sick" from "healthy" (see Supplementary Table 1 for full list of diseased control dog health conditions). However, these controls were not site- or tissue-matched and therefore could not directly test whether dogs can discriminate HSA from benign splenic or vascular lesions. This will be a crucial next step for future research. However, our study did provide an unplanned but highly informative test case. Sample R2 was initially classified as splenic HSA but was later reinterpreted by pathologists as multifocal thrombosis with infarct and hematoma. The submitting institution has since indicated that this case is likely to be reclassified pending completion of a formal pathology review, although at the time of publication a final diagnostic determination has not yet been made. The dogs' performance on this sample was marked: one dog scored 0 % in their session with R2 as the designated HSA sample, and overall accuracy across repeated presentations (with reinforcement) was only 38.9 %, noticeably lower than their performance on confirmed HSA samples (55.5–91.4 %). This suggests that the dogs may have been more accurate than the initial pathology reports in identifying the true underlying condition. Cases such as this sample highlight the potential of VOC-based approaches to complement conventional diagnostics, especially in instances where histopathology yields equivocal or conflicting results. The fact that canine olfaction appeared to detect differences that could not be agreed upon by experienced pathologists underscores the promise of VOC profiling as an adjunct tool in challenging diagnoses.

When considering the odor profile of HSA, our dataset included HSA from splenic, cardiac, and other visceral sites, and dogs were able to detect each with comparable success. This could indicate the presence of a generalized odor signature across anatomic origins of HSA, or alternatively, may reflect that dogs had been exposed to all three subtypes during training and thus learned to recognize the odor signature of each. Because the number of cases for each HSA subtype was modest and uneven across collection sites, Model 3 had limited statistical power, and subtype-specific estimates should therefore be interpreted cautiously. Importantly, this does not affect the broader preliminary conclusion that dogs can detect an odor signature associated with HSA. It should also be noted that cutaneous HSA was not tested in this study. Cutaneous HSA is relatively rare and presents differently to visceral HSA (Schultheiss, 2004). We focused here on splenic, cardiac, and visceral HSA because they are the most common and clinically dangerous forms in dogs, but future studies may wish to evaluate whether cutaneous HSA produces a similar or divergent odor signature.

Another consideration is whether detection is impacted by the breed of the affected dog, given that most samples were obtained from the GRLS cohort. The test sample sets predominantly comprised Golden Retrievers; however, two matched sets from VHUP included other breeds (e.g., Labrador Retriever, Mixed Breed). The dogs' ability to detect HSA in these cases suggests that the odor signature is not limited to a single breed, although broader validation across breeds remains warranted. The majority of samples utilized in this study were sourced through the GRLS, which collects and banks specimens from dogs across multiple veterinary clinics throughout the United States. While consistent long-term storage at GRLS could contribute to some shared background odor, these potential effects were evenly distributed across diagnostic categories (HSA, healthy, diseased). Because sample origin and storage conditions did not align with disease status (e.g., all HSA from one site and all controls from another), we do not believe that the detection dogs could have relied on site- or storage-related cues to achieve successful discrimination. Taken together, these findings provide preliminary proof-of-concept evidence that dogs can detect a serum odor signature associated with HSA.

The next step is chemical characterization of this VOC signature to enable translation into scalable diagnostic methods. Gas chromatography–mass spectrometry (GC-MS) has been widely used in VOC research (Shirasu and Touhara, 2011), and more advanced multidimensional chromatographic approaches provide greater specificity for analyzing complex biological mixtures (Phillips et al., 2013; Selyanchyn et al., 2013). Pairing these analytical techniques with canine validation would enable identification of the compounds underlying the HSA odor profile. Dogs may also play a valuable role in validating pseudo-odor training aids and testing biosensor prototypes (Guest et al., 2021). Although trained dogs are likely not feasible for widespread screening, their demonstrated sensitivity provides a biological benchmark confirming that HSA emits a detectable odor profile. Once identified, these VOCs could be quantified using chromatographic and sensor-based approaches and integrated into diagnostic platforms for routine screening or early detection of HSA, particularly in breeds or age groups at higher risk.

In conclusion, this study provides preliminary evidence that dogs can reliably detect a serum odor of HSA under double-blind conditions. These findings provide a foundation for chemical characterization of the HSA odor signature and the eventual development of minimally invasive diagnostic tools to improve outcomes for dogs affected by this aggressive cancer. A field that began in human oncology is now expanding to veterinary oncology, with the promise of improving early diagnosis for dogs and potentially offering translational insights relevant to human medicine.

Author contributions

CMO, CW, AM, and MB conceived and designed the study. CW oversaw and ran the study. SH and JK assisted with study execution. CW, SH, and JK drafted the first version of the manuscript. CW conducted the statistical analyses. MB, AM, and CMO provided critical revisions to the manuscript. All authors reviewed and approved the final version.

CRediT authorship contribution statement

Clara Wilson: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Samantha Holden:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Julianna King:** Writing – review & editing, Project administration, Data curation. **Amritha Mallikarjun:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Molly Buis:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Cynthia M. Otto:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2025.106522.

Data availability

The raw data generated and analyzed during this study are available in the supplementary file accompanying this article.

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