Performance of IDEXX Cancer Dx testing for detection of lymphoma and corresponding phenotype in dogs

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Introduction

Lymphoma is one of the most common cancers in dogs, accounting for up to 24% of all diagnosed canine cancers and 83% of canine haematopoietic tumors.[1] The estimated annual incidence is approximately 160 per 100,000 dogs of all ages.[1] Lymphoma is more common in middle-aged to older dogs, with a median age of 8.8 years at first diagnosis.[2] Breed predisposition to higher risk and younger age of onset have been reported for bullmastiffs, boxers, Bernese mountain dogs and others.[2] Most cases of canine lymphoma are terminal, with less than 5% of dogs experiencing a cure.[1,3] Chemotherapy is the mainstay of treatment, and a range of protocols, including multi-agent and single-agent protocols, can be used to induce remission in 80%–90% of dogs.[4,5] If untreated, the median survival time in dogs is 4–8 weeks; chemotherapy can extend survival times to 6–12 months, with 20% of dogs living 2 years after diagnosis.[6] Phenotype is the most important prognostic indicator influencing survival times in dogs; the median survival time of aggressive B-cell lymphoma is about twice that compared to aggressive T-cell lymphoma.[6]

Multicentric lymphoma is the most common presentation (83%), and cutaneous (12%) or other extranodal sites (5%) are less common.[7] Cytology is a common diagnostic technique with high sensitivity (92.6%) and specificity (89.4%).[10] To guide prognosis and treatment, confirmation of an inconclusive cytology result with histology or PCR for Antigen Receptor Rearrangement (PARR), identification of subtype with histology and immunohistochemistry, or phenotyping with PARR or flow cytometry may be pursued.[1,8–11] In two studies, approximately 25% of lymph node aspirates submitted to a laboratory were non-diagnostic, delaying diagnosis and treatment.[12,13] A combination of these techniques is sometimes necessary due to the potential for equivocal results.

IDEXX Cancer Dx™ testing utilises multimodal diagnostic technologies to sensitively and specifically. detect circulating biomarkers for canine lymphoma. IDEXX Cancer Dx testing overcomes many of the current diagnostic challenges by detecting lymphoma on a blood specimen and potentially providing phenotype information to guide clinical decision-making and client conversations around prognosis and treatment. This test is appropriate for use in dogs suspected of having lymphoma and in apparently healthy animals at increased risk for cancer (senior dogs aged 7 and above as well as dogs categorised as an at-risk breed aged 4 and above) as part of a preventive care visit.

Breeds at increased risk for lymphoma

Increased risk of cancer (overall), including lymphoma

+ Golden retriever[14]
+ French bulldog[2]
+ Beagle[15]
+ Boxer[15]
+ Miniature schnauzer[15]
+ Bernese mountain dog[16]
+ Flat-coated retriever[16]
+ Scottish terrier[16]
+ Bullmastiff[16]

Increased risk of lymphoma

+ Labrador retriever[17]
+ Rottweiler[18]
+ Doberman pinscher[19]
+ English bulldog[1]

Methods and patient population

Specimens were collected from two private specialty groups and one university to evaluate dogs with confirmed lymphoma, dogs with non-lymphoma diseases and healthy dogs using IDEXX Cancer Dx testing. Confirmed lymphoma was defined as either histology with immunohistochemistry or as cytology with immunocytochemistry, PARR or flow cytometry. Dogs were excluded from the sensitivity and specificity analysis if they had received chemotherapy, steroids or immunosuppressive therapy within one month of specimen collection. For sensitivity and specificity analysis, 105 treatment-naïve dogs with confirmed lymphoma, 73 dogs with other active disease processes and 156 apparently healthy dogs were included. The other active disease category included 61 dogs diagnosed with various non-lymphoma tumors and 12 dogs with various inflammatory diseases. Apparently healthy dogs had a normal physical examination and no significant findings on a CBC and comprehensive biochemistry. The B-cell vs. T-cell differentiation included 83 dogs from the sensitivity and specificity analysis with an

IDEXX Cancer Dx™ phenotyping result and an additional 24 dogs with IDEXX Cancer Dx results and undergoing treatment for lymphoma or with an unknown treatment history for a total of 107 dogs.

Collected specimens were run in singlicate across multiple reagent lots for each assay modality. Results were analysed for each reagent lot combination, which provided 4 potential results per patient. Assay sensitivity, specificity and predictive values for detecting lymphoma were estimated by logistic regression.[20] Relevant model coefficient standard errors were used to construct 95% confidence intervals for each statistic. Assay sensitivity and specificity to labelling phenotype were also estimated by logistic regression using separate models for B-cell and T-cell since they are not mutually exclusive. The 95% confidence interval for this statistic was estimated by bootstrap resampling of the data with n = 1,000.

The effects of interfering substances on assay performance were evaluated by comparing the distributions of assay concentrations between groups of specimens with various levels of interferent. Field specimens for 10,514 canine patients with paired IDEXX Cancer Dx and interfering substance results were used for this analysis. Comparison groups were defined as N, 1+, 2+, 3–4+ for haemolysis; N, 1+, 2–4+ for lipaemia and bilirubin; and < 0.1, 0.1, 0.2, > 0.2 for total bilirubin. For each interferent, each group was compared to the lowest group (N or < 0.1) by comparing the proportions of IDEXX Cancer Dx concentrations exceeding critical assay thresholds. 95% confidence intervals of this statistic were again estimated by bootstrap resampling, n = 1,000.

Sensitivity and specificity for detecting lymphoma

Distribution	Multicentric	98 (93.3%) (94 aggressive, 4 indolent)
	Cutaneous/mucocutaneous	3 (2.9%)
	Mediastinal	3 (2.9%)
	Other extranodal	1 (0.9%)
Phenotype	B	77 (73.3%)
	T	28 (26.7%)
Stage	I	2 (3.6%)
	II	1 (1.8%)
	III	40 (71.4%)
	IV	9 (16.1%)
	V	4 (7.1%)
Method of phenotyping	PARR	25
	Flow cytometry	45
	Unknown flow cytometry or PARR	28
	Immunocytochemistry	5
	Immunohistochemistry	2

Table 1. Characterisation of 105 lymphoma dogs included in the sensitivity and specificity analysis.

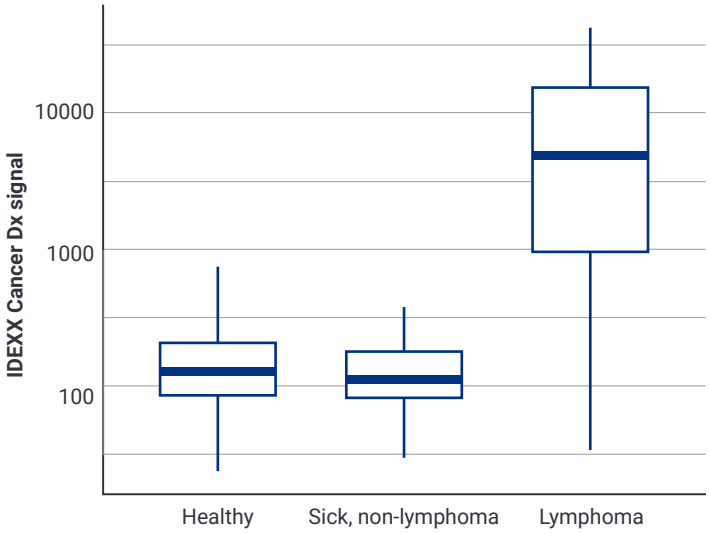


Figure 1. IDEXX Cancer Dx testing detected 79.3% (95% CI: 70.5%, 86.0%) lymphoma cases with a specificity of 98.9% (95% CI: 96.2%, 99.7%).

Differentiating B-cell from T-cell lymphoma

IDEXX Cancer Dx testing returned a phenotyping result in 56% of cases with a result indicating lymphoma. IDEXX Cancer Dx testing returned a phenotype in 65.5% (95% CI: 54.7%, 74.8%) of known B-cell lymphomas with a specificity of 91.3% (95% CI: 71.1%, 97.8%) and in 8.7% (95% CI: 2.2%, 28.9%) of known T-cell lymphomas with a specificity of 98.8% (95% CI: 92.0%, 99.8%).

Phenotype by flow, ICC, PARR, IHC	IDEXX Cancer Dx B-cell	IDEXX Cancer Dx T-cell	IDEXX Cancer Dx indeterminate
B-cell	55	1	28
T-cell	2	2	19

Table 2. Phenotype results determined by IDEXX Cancer Dx testing and reported phenotypes from traditional methods.

Intrinsic specimen interference

Mild/moderate lipaemia, icterus or haemolysis had no significant effect on lymphoma detection. Observed changes in biomarker distributions that were associated with interferents were well below critical decision thresholds.

Discussion

IDEXX Cancer Dx testing is a highly sensitive and specific diagnostic for lymphoma that overcomes current challenges in diagnosing lymphoma. A result that is consistent with lymphoma on this diagnostic provides the necessary confidence to initiate treatment in patients with clinical suspicion of lymphoma. Preliminary data suggests that other lymphoproliferative neoplasia, including acute and chronic leukaemias

and myeloma-related disorders, may have IDEXX Cancer Dx™ results consistent with lymphoma due to shared lymphoid cell origin. If the clinical presentation is not consistent with lymphoma and suggestive of another lymphoproliferative neoplasia, clinical information and potentially further diagnostics should be used to inform the final diagnosis. Two patients with other cancers had IDEXX Cancer Dx results consistent with lymphoma. The first was diagnosed with metastatic mast cell disease based on the histology of a primary lesion and cytology of a lymph node approximately one year later. Additional investigation into the case is ongoing, including PARR performed on a blood specimen from the patient, which revealed a clonal B-cell population. The second case was diagnosed with a suspected splenic sarcoma based on histology. Additional investigation into this case is also ongoing, including a review of histology, which is concerning for an extramedullary plasma cell tumour.

In healthy dogs, an IDEXX Cancer Dx diagnosis of lymphoma is rare, with < 1 in 1,000 healthy dogs expected to receive a lymphoma diagnosis in a year. For patients with an increased risk of cancer, results consistent with lymphoma may suggest early detection of cancer. Due to the very low prevalence in healthy dogs, false-positive results can also occur in healthy patients screened for lymphoma despite the very high specificity. Careful physical examination and a monitoring plan is recommended to diagnose lymphoma early in healthy patients.

IDEXX Cancer Dx testing is a minimally invasive blood test to detect lymphoma and provide phenotyping. Results were available in 66% of dogs with B-cell lymphoma. Biological differences between lymphomas, anatomic location and tumour subtype may impact the frequency of both lymphoma and phenotyping results. As with other lymphoma diagnostics today, if a strong suspicion of lymphoma remains in an IDEXX Cancer Dx result that is inconsistent with lymphoma, additional workup with diagnostics such as cytology or histology is recommended to obtain a definitive diagnosis.

Conclusion

IDEXX Cancer Dx™ testing offers a rapid and highly reliable diagnostic to detect lymphoma earlier in patients with suspected lymphoma or for those dogs at increased risk of cancer due to age or breed using commonly obtained specimens. IDEXX Cancer Dx testing also offers an opportunity to obtain a phenotype on the same specimen with high accuracy at no additional cost to provide treatment and prognostic information.

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Acknowledgement

We would like to thank Ethos Veterinary Health, MedVet, and University of Guelph—Ontario Veterinary College for their invaluable contribution to the sample sets used in this study. Their support and collaboration were essential to the successful completion of this research.

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