一 般 選 抜
2025年10月・2026年4月入学　東京農工大学大学院農学府博士課程共同獣医学専攻
October 2025/ April 2026 Entrance Cooperative Division of Veterinary Sciences, Tokyo University of Agriculture and Technology
入 試 問 題 (Academic achievement test)　外国語（英語）(English)
15 枚のうちの 1, 1 out of 15

Article [1] Read the passage and answer the questions Q1-1 to Q1-5. On the answer sheet, write the question number followed by your answer to it.

Title: An open science study of ageing in companion dogs

ABSTRACT

The Dog Aging Project (DAP) is a long-term longitudinal study of ageing in tens of thousands of companion dogs. The domestic dog is among the most variable mammal species in terms of morphology, behaviour, risk of age-related disease and life expectancy. Given that dogs share the human environment and have a sophisticated healthcare system but are much shorter-lived than people, they offer a unique opportunity to identify the genetic, environmental and lifestyle factors associated with healthy lifespan. To take advantage of this opportunity, the DAP will collect extensive survey data, environmental information, electronic veterinary medical records, genome-wide sequence information, clinicopathology and molecular phenotypes derived from blood cells, plasma and faecal samples. Here, we describe the specific goals and design of the DAP and discuss the potential for this open-data, community science study to greatly enhance understanding of ageing in a genetically variable, socially relevant species living in a complex environment.

INTRODUCTION

Age is the strongest risk factor for most major causes of death and disability in developed nations. Although many aspects of ageing are shared across all individuals, the rate and order of various forms of functional decline and onset of disease vary greatly. The mechanisms underlying individual trajectories of ageing are influenced by complex combinations of genes, environment and lifestyle that remain poorly understood. Most of what we know about the biology of ageing comes from laboratory studies of inbred, laboratory-adapted species, including yeast, worms, flies and mice. While these laboratory models have facilitated rapid progress in identifying evolutionarily conserved mechanisms of ageing, we cannot be certain of the extent to which these findings reflect causal determinants of ageing in outbred populations in heterogeneous environments. To better understand how genes and environment shape ageing in non-human animals outside the laboratory and to generate knowledge that could readily translate to human ageing, we have turned to the companion dog as a powerful animal model that shares the human environment but ages more rapidly. Here, we describe the DAP, an open-data long-term longitudinal study of ageing in tens of thousands of companion dogs. The scientific objectives of this study are to identify the genetic, environmental and lifestyle factors that influence ageing in dogs, to discover the underlying molecular mechanisms by

which they do so and to test potential ways to increase the duration of healthy lifespan in dogs.

We have designed the DAP to achieve our overarching scientific goals while also ensuring the well-being of all study participants, complying with all appropriate regulations, meeting the highest ethical standards and creating an open-data platform. The DAP is an interdisciplinary, open-data, community science project that consists of a team of more than 100 staff, students, faculty and veterinarians from more than 20 academic institutions, along with over 30,000 canine participants and their owners. Together, we are creating an enormous resource of health, behavioural and lifestyle data gathered from owners and veterinarians, complemented with detailed molecular and environmental profiling. The DAP includes observational studies, combining both retrospective cross-sectional and prospective longitudinal data, as well as a randomized, placebo-controlled clinical trial for healthy ageing. Data and biospecimens will be collected annually and made available as a public resource. Moreover, the study is designed in a way such that independent researchers can create integrated ancillary studies to benefit from the powerful DAP infrastructure.

The companion dog is an ideal animal in which to study biological ageing. Dogs are one of the most variable animal species known in size, shape and behaviour. Moreover, like humans, individuals vary in life expectancy and the spectrum of diseases they are likely to encounter. Companion dogs experience nearly every functional decline and disease of ageing that people do, and, importantly, these diseases are diagnosed and treated within a sophisticated healthcare system that parallels human healthcare in many ways. Companion dogs age approximately seven to ten times faster than humans, allowing for longitudinal and interventional study in the timeframe of just a few years. They also share the human physical and chemical environment, a major determinant of ageing that cannot be adequately modelled in laboratory studies. For all of these reasons, findings from ageing companion dogs could readily translate to human ageing. Finally and perhaps most importantly, companion dogs are considered as family by hundreds of millions of people around the world. Simply put, people love dogs. This deep commitment allows the DAP to engage the general public in science in a way that few research projects can and enables the project to collect detailed, nuanced information about each participant dog's unique life experiences in a way that cannot be duplicated in any other species. This relationship, unparalleled in other animal models, provides intrinsic value to the research beyond what is learned about human ageing.

DESIGN OF THE DAP

The power of the DAP lies in our ability to capture the breadth of diversity of companion dogs and to collect a rich array of data about each dog. The greater the diversity, the greater the opportunity to characterize the age trajectory of diseases, to identify biomarkers and to discover

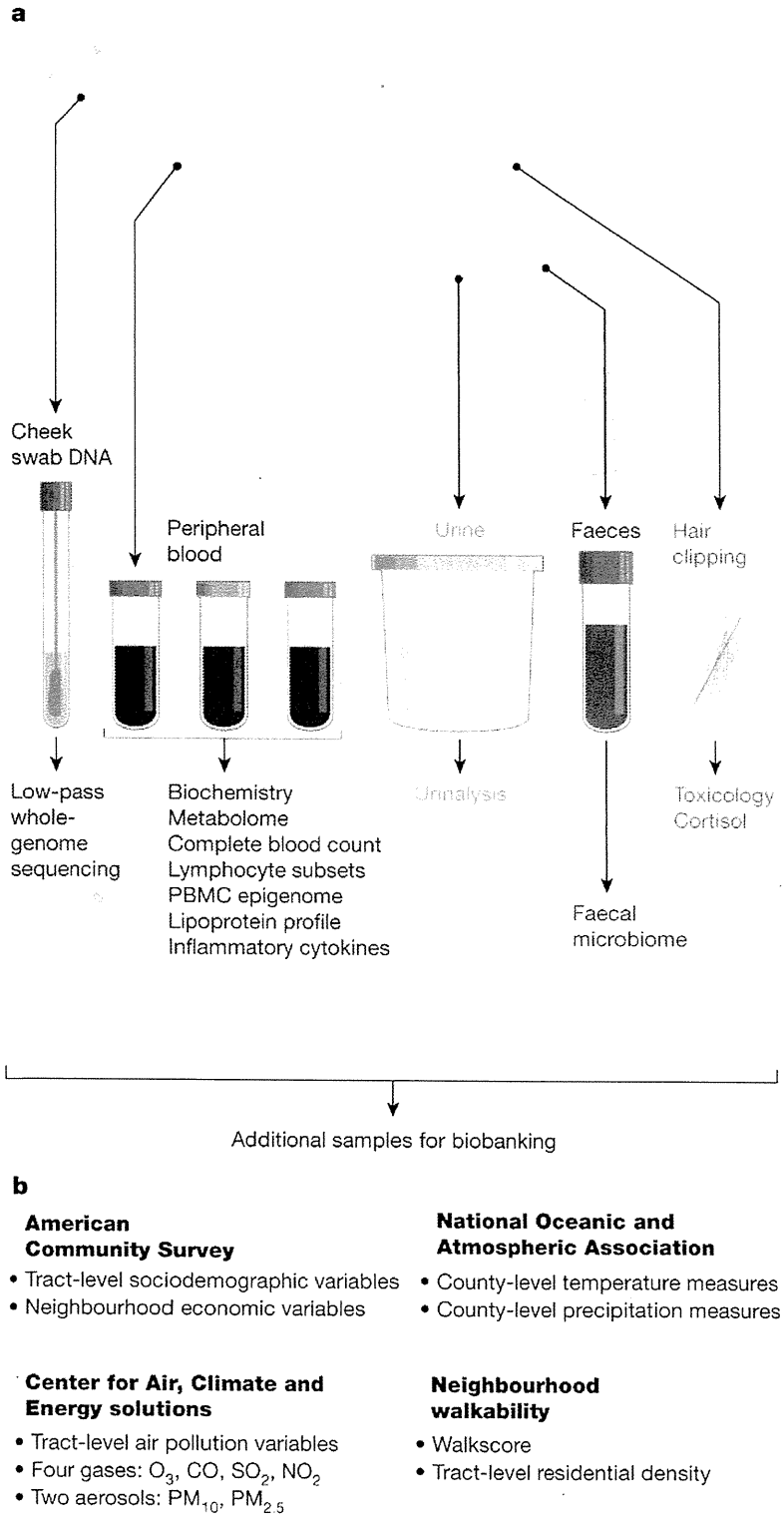

Fig. 1: Biospecimen and environmental measures.

genetic and environmental risk factors for disease outcomes. The target study population consists of dogs of all breeds (both purebred and mixed breed), ages, sizes and sexes (males and females, intact and sterilized).

The DAP has four primary scientific aims. These include (1) characterizing ageing in companion dogs on three separate axes: multimorbidity, frailty and inflammageing; (2) using low-coverage whole-genome sequencing with imputation on at least 10,000 dogs to analyse the genetic architecture of age-related traits in dogs; (3) collecting metabolome, epigenome and microbiome profiles to develop biomarkers of ageing in dogs and to better understand the mechanisms by which genetic, environmental and lifestyle variation influence ageing; and (4) carrying out a randomized, double-masked, placebo-controlled study to determine the effects of rapamycin on lifespan and healthspan in large-breed, middle-aged dogs.

DATA COLLECTION

Biospecimen kits include vials for collection of whole blood, plasma, serum, urine, hair and faeces as well as dried blood spot cards (Fig. 1). These kits are shipped to a commercial veterinary reference laboratory, where routine clinicopathologic assays are performed immediately. Biospecimens are then forwarded to DAP laboratories for analysis of metabolome, microbiome, epigenome and flow cytometry profiles, as well as inflammageing assays. Residual biospecimens are sent to the DAP Biobank, housed at the Cornell Veterinary Biobank, and made available for analysis by the research community.

CONCLUSION

The DAP is an ambitious research initiative, creating a resource with the power to transform veterinary medicine, ageing research and many scientific and non-scientific fields of enquiry. Similar to all longitudinal studies, the success of the DAP depends in large part on strong and enduring relationships with many stakeholders, including participating dog owners, veterinarians and researchers. To accomplish this, we have devoted considerable resources to building strong, diverse communication pipelines; actively engaging with participants, veterinarians and scientists; and providing open access to the wealth of data produced by this project. We are also putting great effort into participant retention, and we are redoubling our efforts to capture the diverse dimensions of US dog owners who are not yet adequately represented in our study population. Through these efforts, the DAP is establishing the foundation for an innovative community science approach to ageing research in dogs. We are excited to use the DAP as a platform on which to build a truly transformative, interdisciplinary and integrated research programme.

(Nature 602: 51–57, 2022 modified)

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15　枚のうちの　5, 5　out of 15

Q1-1: Point out problems with conventional aging model studies in no more than five lines of English.

Q1-2: Explain the member attributes of the DAP and the number of dogs involved. Answer the question in no more than five lines of English.

Q1-3: What is the research methodology of the DAP? Answer the question in no more than five lines of English.

Q1-4: What are the scientific purposes of DAP? Answer the question in around five lines of English.

Q1-5: Explain the relevance of the DAP to human aging research in no more than five lines of English.

Article [2] Read the passage and answer the questions Q2-1 to Q2-5. On the answer sheet, write the question number followed by your answer to it.

Title: Bispecific antibodies targeting two glycoproteins on SFTSV exhibit synergistic neutralization and protection in a mouse model

ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease with a high fatality rate of up to 30% caused by SFTS virus (SFTSV). However, no specific vaccine or antiviral therapy has been approved for clinical use. To develop an effective treatment, we isolated a panel of human monoclonal antibodies (mAbs). SF5 and SF83 are two neutralizing mAbs that recognize two viral glycoproteins (Gn and Gc), respectively. We found that their epitopes are closely located, and we then engineered them as several bispecific antibodies (bsAbs). Neutralization and animal experiments indicated that bsAbs display more potent protective effects than the parental mAbs, and the cryoelectron microscopy structure of a bsAb3 Fab–Gn–Gc complex elucidated the mechanism of protection. In vivo virus passage in the presence of antibodies indicated that two bsAbs resulted in less selective pressure and could efficiently bind to all single parental mAb-escape mutants. Furthermore, epitope analysis of the protective mAbs against SFTSV and Rift Valley fever virus (RVFV) indicated that they are all located on the Gn subdomain I, where may be the hot spots in the phleboviruses. Collectively, these data provide potential therapeutic agents and molecular basis for the rational design of vaccines against SFTSV infection.

INTRODUCTION

SFTS is an emerging tick-borne infectious disease, resulting in severe clinical symptoms of hemorrhagic fever, encephalitis, and multiple organ failure. This disease has been reported in China, South Korea, Japan, and Vietnam with a fatality rate of 5 to 30%. However, there is currently no vaccine or antiviral therapy available. Although ribavirin exhibits inhibition on SFTSV replication in vitro and in a mouse model, it displayed less effect in a retrospective cohort of patients. Favipiravir (T-705), an RNA-dependent RNA polymerase inhibitor of a broad spectrum of RNA viruses, has shown a higher antiviral efficacy for inhibiting SFTSV replication in vitro or in animal models than ribavirin. However, large-scale clinical trials need to be conducted to fully establish its safety and efficacy.

SFTSV, which has been officially named *Dabie bandavirus* or *Bandavirus dabieense*, is the pathogen that causes SFTS. It was first discovered in China in 2009. SFTSV is classified as a member

of the genus *Bandavirus* in the *Phenuiviridae* family and *Bunyavirales* order. Its genome contains three RNA segments (Small, Medium, and Large) that encode a nucleoprotein, nonstructural protein, envelope glycoprotein, and RNA-dependent RNA polymerase. The Medium segment encodes the precursor of the glycoprotein, which can be further cleaved into Gn and Gc proteins. These two glycoproteins are type I transmembrane proteins. Gn is proposed to be a receptor-binding protein, and Gc is a membrane fusion protein. Both are critical for SFTSV infection. RVFV and Heartland virus (HRTV) are two pathogens in the genus *Phlebovirus* that cause severe human infectious diseases. The structures of the Gn head in SFTSV and RVFV have been determined. They exhibit similar overall structures, composed of three subdomains. However, the homology and arrangement of the subdomains between these two viruses are not identical. Moreover, the structure of the Gn stem region still needs to be explored.

mAbs targeting glycoproteins represent an effective antiviral strategy against SFTSV. To date, three neutralizing antibodies have been identified. MAb4-5 and Ab10 are two neutralizing mAbs screened from a human single-chain variable-region fragment (ScFv) antibody library. Ab10 inhibits SFTSV infection both in vitro and in animal studies, while MAb4-5 exhibits potent inhibition in vitro but displays little protection efficacy in an infected mouse model. A crystal structure shows that the epitope of MAb4-5 is located in subdomain III of the Gn head, and alanine scanning indicates that the epitope of Ab10 may be within subdomain II and the stem region of Gn. A variable domain of the heavy chain of a heavy-chain antibody (VHH) derived from camel, SNB02, fused to a human Fc fragment displays antiviral activity both in vitro and in the mouse model. However, both Ab10 and SNB02 only inhibit SFTSV replication after treating mice for 4 d consecutively. Therefore, a more potent protective antibody or an engineered antibody must be developed for clinical treatment, such as a bsAb that combines two antigen-binding sites of two different antibodies within one molecule. This dual-targeting strategy has been proven to hold greater therapeutic efficacy than parental antibodies in cancer and infectious diseases.

In this study, we identified six human mAbs (SF1, SF5, SF62, SF64, SF71, and SF83) from a SFTS convalescent patient. SF83 bound to Gc, and the other mAbs bound to Gn. Except for the SF62, the other mAbs presented varying neutralizing activities. SF1, SF5, and SF83 exhibit neutralization in both the pseudovirus and the authentic virus systems. Moreover, the crystal structures of antigen–antibody complexes indicate that SF1 binds to the Gn head subdomain III, which is identical to the previously reported MAb4-5. SF5 recognized the Gn head subdomain I, and SF83 bound to Gc domain II. Among these Abs, SF5 presented potent protection in a SFTSV-infected mouse model, and **SF83 exhibited partial protection ability**. Therefore, we engineered four bsAbs with DVD-Ig and IgG-$(ScFv)_2$ designs based on this epitope analysis. Two of the bsAbs exhibited

synergistic neutralizing ability in vitro, and two others displayed protection efficacy in vivo compared to their parental mAbs. In addition, bsAbs drove fewer escape mutants than mAbs at the same concentration level, which further demonstrates the advantages of bsAbs in the defense of SFTSV.

DISCUSSION

SFTSV causes SFTS with a fatality rate of 5 to 30%. However, there are currently neither registered preventive vaccines nor effective therapeutics available. In this study, we identified several mAbs that target glycoproteins on the SFTSV. Among these mAbs, SF5 and SF83 bound to Gn and Gc, respectively, and exhibited neutralization in vitro and protective abilities against SFTSV in a mouse model. We also identified their epitopes by determining the antigen–mAb complex structures and further developed bsAbs in both IgG-$(ScFv)_2$ and DVD-Ig formats based on epitope analysis (Figure 1). Two bsAbs displayed improved potency both in vitro and in vivo. The mechanism of DVD-Ig was revealed by determining the bsAb3 Fab–Gn–Gc complex structure using cryoelectron microscopy. Moreover, bsAbs drive less selective pressure compared to parental mAbs, suggesting the advantages of their clinical use in the future.

In previous studies, two SFTSV-protective antibodies were reported with A129 mice or NCG-HuPBL mice, respectively. However, these two antibodies only display protection when administered to mice for four consecutive days. Moreover, the dosage required is 600 μg/day (30 mg/kg Ab10) or 400 μg/day, respectively. In contrast, 10 mg/kg SF5 and 5 mg/kg bsAb1 or bsAb3 provided complete protection with one dose in our study here. Furthermore, 5 mg/kg of bsAb1 and bsAb3 provided 100% protection with one dose, which further proves the potency of these bsAbs. In our study, an A129 mouse model was used to evaluate the protective efficacy of the antibody. Considering the differences between humans and mice, the SF5 and bsAbs should be further evaluated in a nonhuman primate model in the future.

Antibodies play an essential role in protection against virus infections. Some of them can prevent viral entry into cells or induce lysis of infected cells through antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). The ADCC and CDC effects of SF5, bsAb1, and bsAb3 should be further explored. With its lower somatic hypermutation rates in both heavy chain and light chain, SF5 has a relatively low binding affinity for SFTSV Gn, with both a fast association rate and disassociation rate. However, this mAb shows potent protective efficacy in a SFTSV infection mouse model. Therefore, several approaches can be applied to improve the affinity of SF5. On one hand, a random substitution library should be constructed and screened. One the other hand, structure-based SF5 modification could be performed. Moreover, more mAbs have been identified against SARS-

CoV-2 and influenza virus than bandaviruses. Further screening mAbs targeting this epitope from convalescent patients may also uncover potent protective mAbs with high affinity. SF83 exhibits high affinity in vitro but lower protective efficacy in vivo. The reason may be that purified Gc protein using in the binding affinity is a monomer, and the SF83 epitope is exposed, thereby displaying high affinity. However, the SF83 epitope located in the inner side of Gc domain II when superimposed the SF83 into the SFTSV glycoprotein architecture. A similar situation may happen in vivo that the SF83 epitope may be exposed when the conformation changed; therefore, the protective efficacy is low.

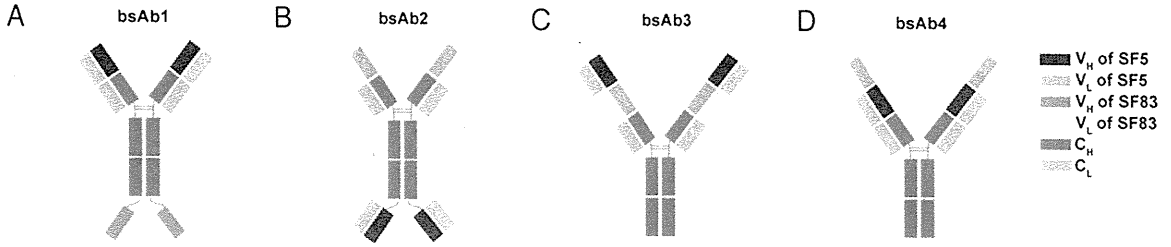

Figure 1 | Design of bsAbs. (A–D) Schematic diagram of four engineering bsAbs. BsAb1 and bsAb2 are in IgG-$(ScFv)_2$ format, whereas bsAb3 and bsAb4 are in DVD-Ig format. V_H: Variable regions in the heavy chain, V_L: Variable regions in the light chain, C_H: Constant regions in the heavy chain, and C_L: Constant regions in the light chain.

(Proc Natl Acad Sci U S A. 121: e2400163121, 2024 modified)

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15　枚のうちの　10, 10　out of 15

Q2-1: How is SFTS transmitted, and what is its mortality rate? Answer the question in no more than three lines of English.

Q2-2: What is the predictive function of the proteins encoded on the second longest RNA segment of the SFTS genome? Answer the question in no more than five lines of English.

Q2-3: What are the characteristics and applications of bispecific antibodies? Answer the question in no more than five lines of English.

Q2-4: Why did the authors design bispecific antibodies with the variable region of SFTS shown in Figure 1? Answer the question in no more than five lines of English.

Q2-5: How do the authors interpret the underlined sentence? Answer in no more than five lines of English.

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15　枚のうちの　11, 11　out of 15

Article [3] Read the passage and answer the questions Q3-1 to Q3-5. On the answer sheet, write the question number followed by your answer to it.

Title: Diagnosis and Classification of Primary Nodal Lymphomas in Dogs: A Consensus of the Oncology-Pathology Working Group

Consensus Recommendations for Lymphoma Diagnosis and Classification

A summary of the subgroup's[*1] recommended diagnostic approach to dogs with suspected nodal lymphomas based upon review of the current literature is presented in Figure 1. Histopathology paired with immunohistochemical staining is required for complete classification of nodal lymphomas in dogs. This is currently the only method by which most nodal lymphoma subtypes, as defined by the WHO system, can be definitively diagnosed. The ideal method for obtaining biopsy specimens for histopathologic evaluation and WHO subtyping has not been conclusively established. However, in the absence of a well-designed study comparing the accuracy of WHO subtype assignment to samples obtained by NCB[*2] vs. surgical lymphadenectomy as a gold standard, it is the consensus of this subgroup that lymphadenectomy specimens should be preferred when complete classification of nodal lymphomas is required, as they provide the greatest amount of morphologic information upon which to establish a diagnosis.

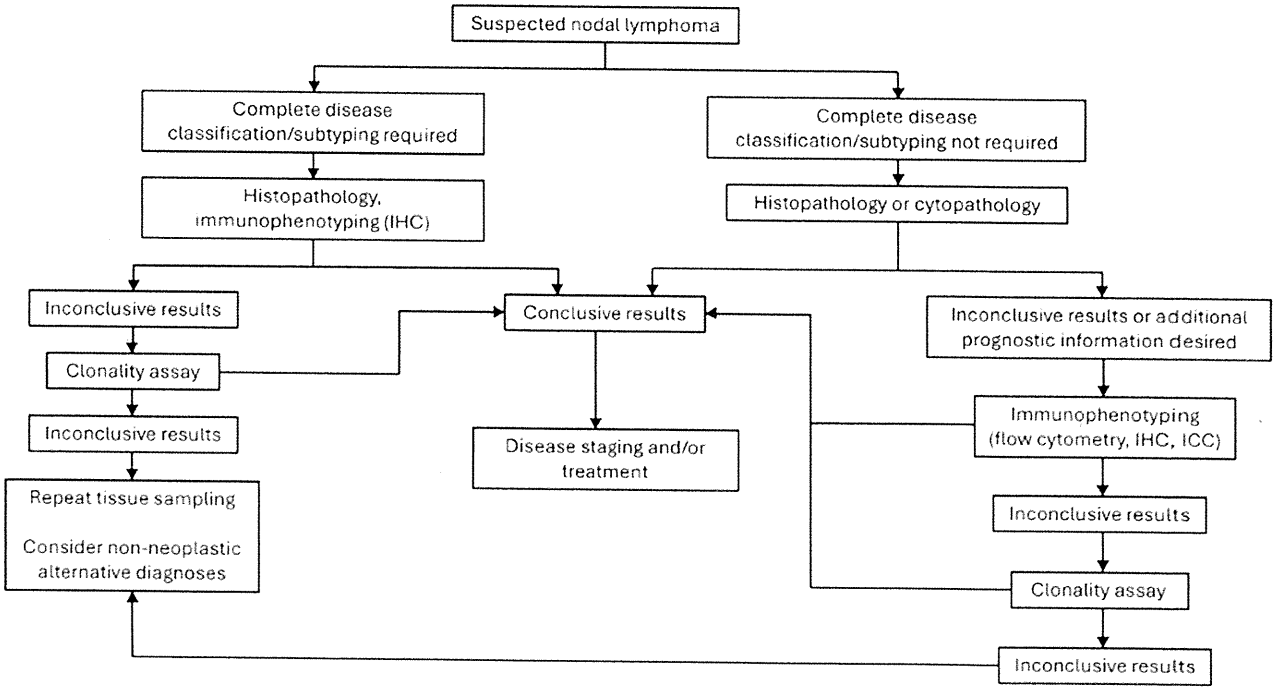

FIGURE 1 | Suggested algorithm for diagnostic evaluation of dogs with suspected nodal lymphomas. IHC = immunohistochemistry; ICC = immunocytochemistry.

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15 枚のうちの 12, 12 out of 15

Cytopathologic evaluation of lymph node specimens collected by FNA is a popular means for diagnosing nodal lymphomas in dogs. The accuracy and sensitivity of cytopathology for diagnosing many lymphomas appear good-to-excellent (> 80%–90%). It is plausible that the diagnostic accuracy of FNA would improve if cytopathologic and immunophenotypic data (such as from FC[*3]) were analysed concurrently. Agreement of cytopathological findings with immunophenotyping results has been reported, although a critical evaluation of this subject, which should include determining the extent of agreement with histopathology and IHC results, is currently lacking for most lymphoma subtypes. It is therefore the consensus of the subgroup that cytopathology can be considered an acceptable means of diagnosing nodal lymphomas, particularly when cytopathology results are consistent with lymphoma in dogs with high prior probability of disease, and when an exacting level of disease subtyping is not necessary to inform treatment decisions. This scenario likely reflects many—if not most—routine clinical practise settings. Histopathology, on the other hand, should be considered imperative in cases where comprehensive diagnostic assessment of a nodal lymphoma is desired. These situations may include clinical trials where entry is restricted to dogs with a specific lymphoma subtype, or routine practise settings when other attempts at diagnosis have failed to clearly identify the disease present. The latter may be especially true when cytopathology results indicate the absence of lymphoma in dogs with high prior probability of disease. Histopathology also should be considered essential for characterising rare or novel lymphoma subtypes.

Immunophenotyping is essential to the complete diagnosis and classification of nodal lymphomas of dogs, as neither histomorphology nor cytomorphology alone accurately distinguishes many lymphoma subtypes from one another. Thus, immunophenotyping should be performed in conjunction with histopathology in all situations where determination of WHO subtype is required. The methods most used for immunophenotyping nodal lymphomas—IHC[*4] and FC—have relative advantages and disadvantages. Neither affords a level of prognostically significant disease classification that is not afforded by the other. This may change as new disease subtypes are fully characterised. For now, however, the consensus of this subgroup is that IHC and FC should be regarded as equally acceptable methods of immunophenotyping a lymphoma. In cases where IHC and FC are not available, ICC[*5] and/or IF[*6] can be considered substitutes, although the latter two methods require additional study before being considered equivalent to IHC and FC in terms of the reliability of the diagnostic information they provide.

It should be noted that, at present, tumour immunophenotype may not affect treatment decisions, as the choice of therapy is often dictated more by the anticipated clinical course (i.e., indolent or aggressive) of the cancer, or simply by the desires of the dog owner. However, the extent

to which immunophenotype should determine the choice of treatment for dogs with nodal lymphomas is currently a subject of much debate in the veterinary oncology community. Some reports suggest that dogs with aggressive T-cell lymphomas may benefit more from chemotherapy protocols enriched with alkylating agents than standard protocols incorporating cyclophosphamide, doxorubicin, vincristine and prednisone. However, randomised trials directly comparing clinical outcomes in dogs with aggressive T- cell lymphomas receiving these two alternative regimens have not been performed. Results that support the use of different treatment regimens for dogs with aggressive B- and T- cell tumours would further solidify the essential role of immunophenotyping in the diagnostic evaluation of dogs with these cancers.

Clonality assays should be used thoughtfully when diagnosing and/or classifying nodal lymphomas in dogs. Because the extent to which they agree with FC and IHC is only moderate, it is the consensus of the subgroup that, whenever possible, clonality assays should not be used as a sole diagnostic test for assigning a lymphoma to a given lymphocyte lineage. Immunophenotyping assays are the preferred diagnostic tests for this purpose. Ideally, clonality assays should be reserved for cases where both morphologic and immunophenotypic characterisation of a lymphoid cell population is inconclusive. In cases where immunophenotyping is impractical (e.g., due to an inability to perform it without acquiring additional diagnostic samples), but morphologic findings strongly support the presence of lymphoid neoplasia, it is reasonable to use clonality assays to determine lineage assignment. It is much less desirable to use clonality assays in the absence of immunophenotyping when morphologic findings are ambiguous or are derived from poor-quality samples. In these situations, the prior probability of lymphoma, as determined by clinical and pathological data, must be considered if ordering a clonality assay, as it significantly affects the assay's positive predictive value. Because the clinical consequences of misdiagnosing lymphoma can be significant, potential causes of false positive and false negative results from clonality assays should also be considered carefully. In cases where the prior probability of disease is only moderate (e.g., other diagnostic or clinical findings suggest an autoimmune or infectious cause for lymph node pathology), and lymph node cytopathology or histopathology results are ambiguous, repeat sampling of a lymph node (ideally combined with immunophenotyping), rather than a clonality assay, is the better means to achieve diagnostic clarity. This is particularly true in cases where histopathology may provide a more representative sample than was afforded by initial cytopathologic sampling.

(Vet Comp Oncol. Online ahead of print, 2025 modified)

*1 The subgroup: the canine lymphoma subgroup organized by the oncology pathology working group

*2 NCB: needle core biopsy

*3 FC: flow cytometry

*4 IHC: immunohistochemistry

*5 ICC: immunocytochemistry

*6 IF: immunofluorescence

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15　枚のうちの　15, 15　out of 15

Q3-1: What biopsy method does this subgroup recommend for complete classification of nodal lymphoma? Answer the question in no more than three lines of English.

Q3-2: How can the diagnostic accuracy of FNA be improved in the diagnosis of nodal lymphoma? Answer the question in no more than three lines of English.

Q3-3: What are the concerns when using ICC and IF in cases where IHC and FC are not available? Answer the question in no more than three lines of English.

Q3-4: What factors does affect to the choice of the treatment plan? Answer the question in no more than three lines of English.

Q3-5: Why should clonality assays be used thoughtfully when diagnosing and/or classifying nodal lymphomas in dogs? Answer the question in no more than three lines of English.