Diagnostic update

# Cardiopet™ proBNP Test: an accurate and reliable quantitative NT-proBNP assay for dogs and cats

## What is NT-proBNP?

B-type natriuretic peptide (BNP) is stored in cardiomyocytes as a prohormone (proBNP) and is released in response to stretch or strain on heart muscle.[1] On release, proBNP is cleaved into a biologically active hormone C-BNP and an inactive amino-terminal fragment (NT-proBNP). The C-BNP hormone acts on blood vessels to induce vasodilation as well as promoting natriuresis and diuresis in the kidney. NT-proBNP has a longer half life than C-BNP, making the quantification of circulating NT-proBNP more amenable for clinical purposes. NT-proBNP is released in proportion to the amount of stretch and stress on the myocardium with concentrations tending to increase with severity of cardiac disease.

## Heart disease in dogs and cats

Approximately 10% of dogs are estimated to have heart disease, with myxomatous mitral valve disease (MMVD) being the most common canine cardiac disorder diagnosed.[2] The disease typically affects small- to medium-sized dogs, such as Cavalier King Charles spaniel (CKCS), Maltese, Chihuahua, Yorkshire terrier, miniature schnauzer, and dachshund. Dilated cardiomyopathy (DCM) is the other major acquired cardiac disease in dogs, which typically affects larger breeds, such as Doberman pinscher, Irish wolfhound, boxer, and Weimaraner. In cats, hypertrophic cardiomyopathy (HCM) is the most common cause of heart disease, with an estimated prevalence of 15% in the general cat population.[3]

## Diagnosing heart disease in dogs and cats

Dogs and cats with early-stage heart disease often present to veterinarians without any clinical signs, and the only abnormality detected on physical examination will be the presence of a murmur or arrhythmia on cardiac auscultation. The presence of a gallop sound may also be detected in cats. In patients where a murmur is heard on auscultation, it is important to establish whether the murmur is caused by an underlying cardiac disorder or is an innocent murmur. A smaller proportion of cases with cardiac disease will present with clinical signs of heart failure, which may include respiratory distress in dogs and cats or coughing in dogs.

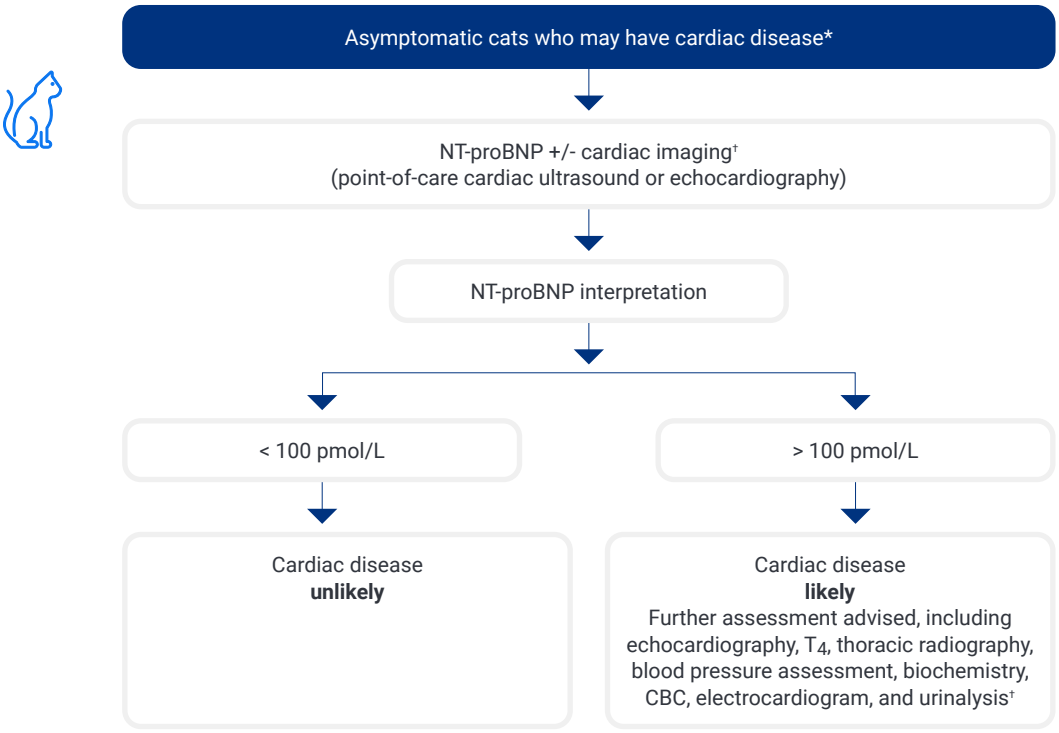
The most definitive way to diagnose structural heart disease in dogs and cats is with echocardiography performed by a veterinary cardiology specialist.[2,3] However, access to a veterinary cardiologist may not be feasible for all patients, and so measurement of NT-proBNP can be a highly informative, cost-effective alternative, especially in the context of screening cats for subclinical disease as well as providing insights as to whether dogs and cats with respiratory distress have an underlying cardiac or respiratory disorder.

## How can the Cardiopet proBNP Test help?

Measurement of NT-proBNP with the Cardiopet™ proBNP Test can be helpful in three key clinical scenarios:

### Does the cat have subclinical (occult) cardiac disease?

Approximately 15% of cats (1 in 6) have heart disease, but not all cases will present with a heart murmur.[3–5] On the other hand, 1 out of 4 apparently healthy cats may have a murmur, but less than half of these cats will have evidence of cardiomyopathy by echocardiogram.[4–7] Consequently, it is difficult to accurately assess whether a cat has subclinical heart disease based on clinical examination alone. The measurement of NT-proBNP may provide supportive information to assist in the timely and efficient assessment of cardiac disease risk in senior cats as part of their routine, annual health check or as part of a preanaesthetic health evaluation.[8] Healthy cats with an NT-proBNP > 100 pmol/L are at increased risk of having a subclinical cardiomyopathy, and further cardiac evaluation with an echocardiogram is recommended, especially if they are male, overweight, or have a murmur grade ≥ 3/6 (figure 1).[9,10]



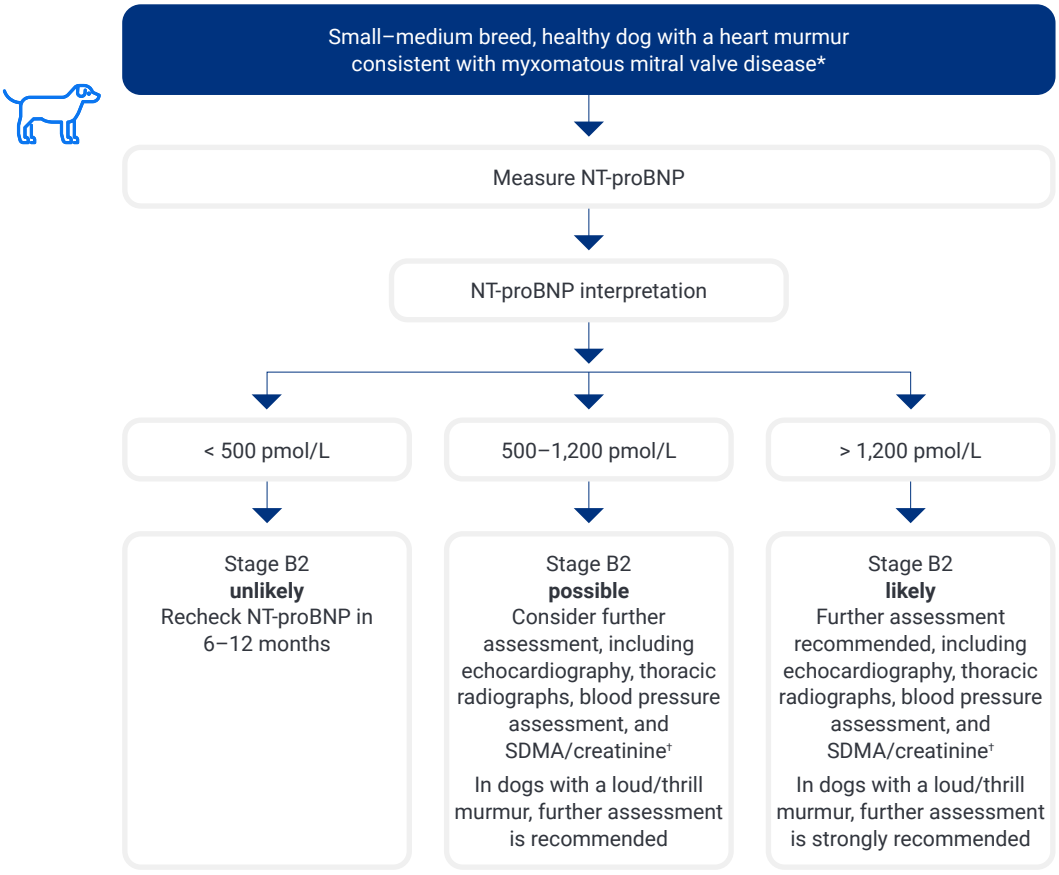

*Asymptomatic cats that may be at an increased risk of cardiac disease include cats with a murmur, arrhythmia, or gallop sound detected on cardiac auscultation.

†Echocardiography is the gold-standard technique for the assessment of cardiac structure and function. Cats with an increased left atrial size +/- left ventricular hypertrophy detected by point-of-care cardiac ultrasound and a NT-proBNP result > 100 pmol/L are likely to have cardiac disease. Consider patient and client factors as part of a spectrum of care approach to diagnostic selection.

Figure 1: Diagnostic algorithm describing the use of NT-proBNP to assess asymptomatic cats for the presence of subclinical heart disease.

## Does the small–medium breed, healthy dog with a murmur and suspected MMVD have stage B1 or B2 disease?

Dogs with MMVD will often present without clinical signs, and the only abnormality detected on clinical examination may be a systolic murmur. On echocardiogram, dogs with a heart murmur but no signs of cardiac remodeling are classified to have stage B1 heart disease. Many dogs will ultimately develop echocardiographic evidence of left atrial and ventricular enlargement, defined as stage B2 heart disease, at which point medical intervention is recommended to delay the onset of cardiac failure.[2] At initial presentation, it is not possible to establish whether the dog is in stage B1 or B2 by physical examination alone, and echocardiography is required to definitively stage the heart disease. Thoracic radiographs are recommended when echocardiography is unavailable. However, not all patients have access to echocardiography or radiography, and in this scenario, the measurement of NT-proBNP can be used to assess the likelihood of stage B2 disease. When imaging is available, NT-proBNP can be a helpful additional tool to inform the assessment of equivocal cases and as a baseline for future trending. Published studies suggest that small–medium breed, healthy dogs with a murmur consistent with MMVD are unlikely to have stage B2 disease if their NT-proBNP concentration is below 500 pmol/L. Whereas, dogs with NT-proBNP above 1,200 pmol/L are likely to have stage B2 disease (figure 2).[11,12]



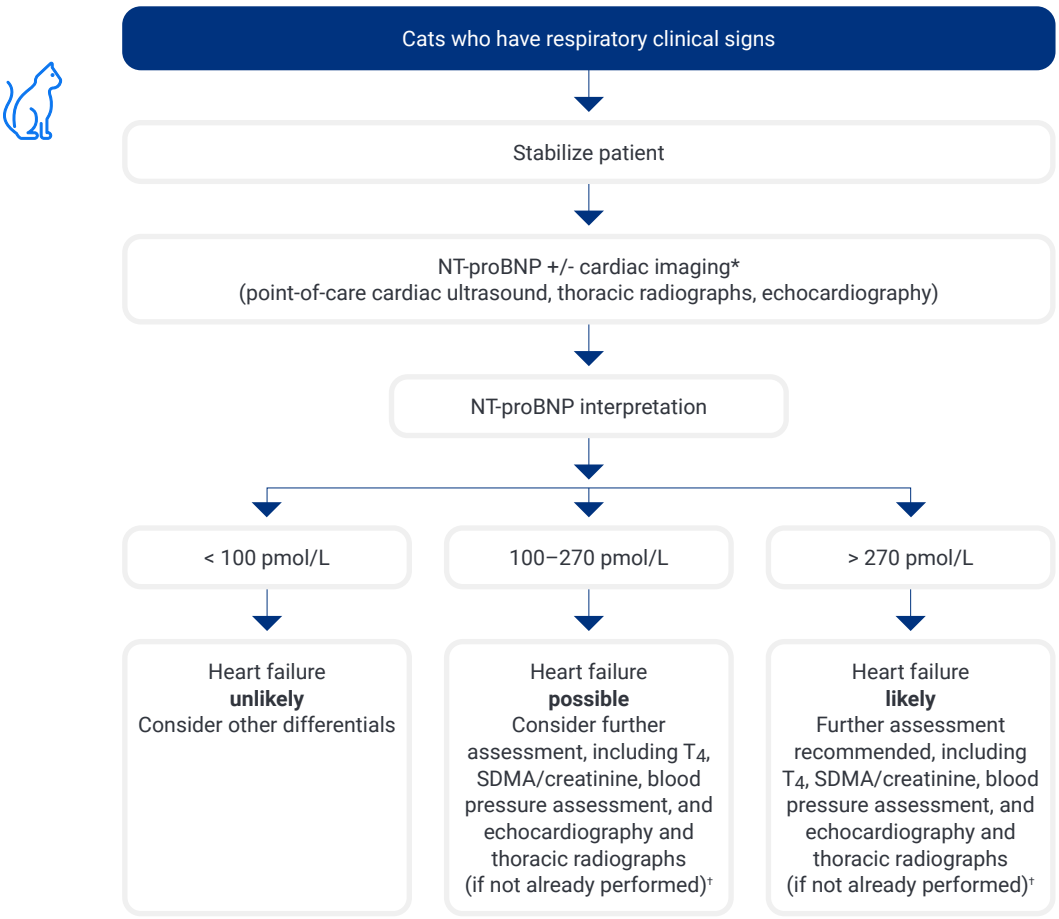

*Echocardiography is the gold-standard technique for the assessment of cardiac structure and function. Thoracic radiographs and measurements taken from them, including vertebral heart score (VHS) and vertebral left atrial size (VLAS), may provide information on heart size. Consider patient and client factors as part of a spectrum of care approach to diagnostic selection.

†Further assessment may include thoracic radiography, echocardiography, blood pressure assessment, CBC, biochemistry, electrocardiogram, infectious disease testing, urinalysis, and abdominal ultrasonography.

Figure 2: Diagnostic algorithm describing the use of NT-proBNP to assess the likelihood of stage B2 disease in small–medium breed, healthy dogs with a heart murmur consistent with MMVD.

## Is cardiac disease the cause of the dog's or cat's breathing difficulties?

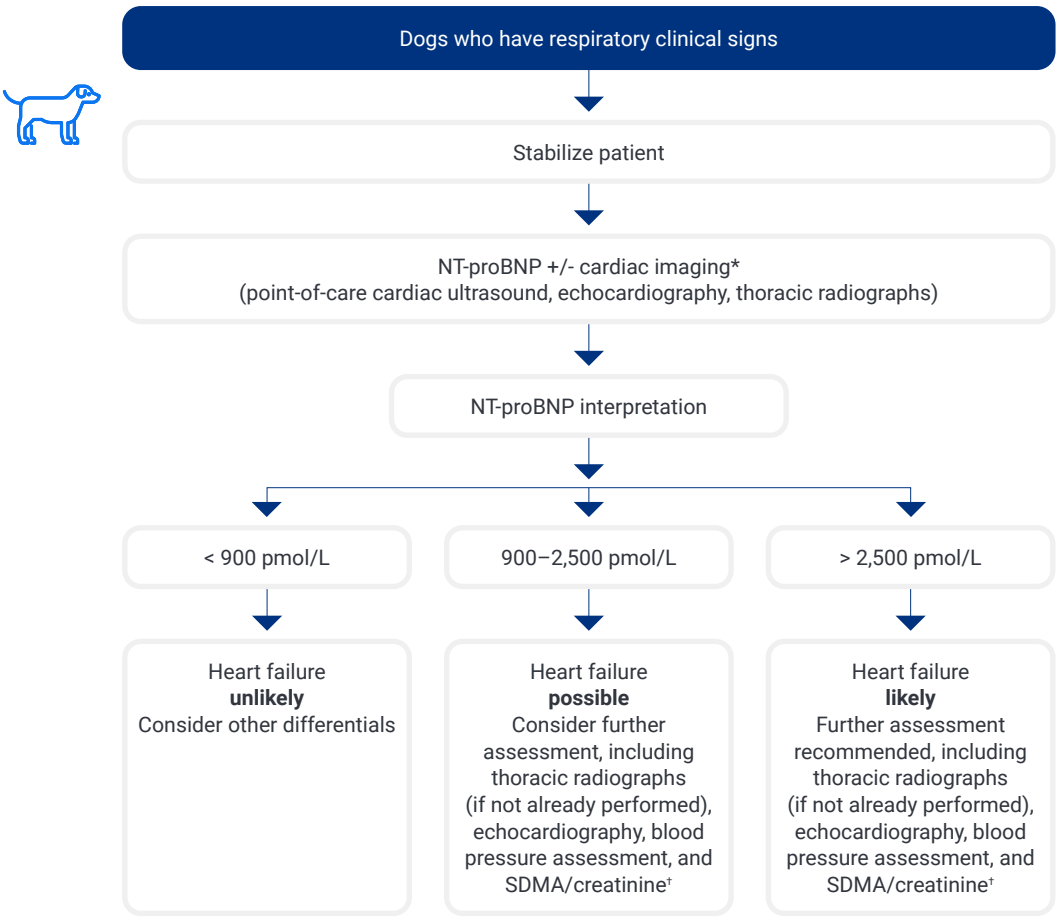
Dogs and cats in respiratory distress often present as an acute clinical emergency. The underlying cause of the clinical signs can be difficult to establish based purely on physical examination. The measurement of NT-proBNP may provide valuable supportive information to help differentiate whether the respiratory distress is caused by primary cardiac or respiratory disease. A value of > 270 pmol/L in cats (figure 3)[13] and > 2,500 pmol/L in dogs (figure 4)[14] with breathing difficulties is strongly suggestive that cardiac failure, rather than respiratory disease, is the cause of the clinical signs. The upper cut-off for NT-proBNP has changed from 1,800 to 2,500 pmol/L following a detailed review of Cardiopet™ proBNP Test data, NT-proBNP publications, and input from cardiology specialists.




*Echocardiography is the gold-standard technique for the assessment of cardiac structure and function. Cats with an increased left atrial size +/- left ventricular hypertrophy detected by point-of-care cardiac ultrasound and a NT-proBNP result > 100 pmol/L are likely to have cardiac disease. Thoracic radiographs recommended for stabilized patients with dyspnea and tachypnea. Consider patient and client factors as part of a spectrum of care approach to diagnostic selection.

†Further assessment may include echocardiography, $T_4$, thoracic radiography, blood pressure assessment, biochemistry, CBC, electrocardiogram, and urinalysis.

Figure 3: Diagnostic algorithm describing the use of NT-proBNP to assess the likelihood of heart failure in cats with respiratory clinical signs.




*Echocardiography is the gold-standard technique for the assessment of cardiac structure and function. Thoracic radiographs recommended for stabilized patients with dyspnea, tachypnea, and coughing. Consider patient and client factors as part of a spectrum of care approach to diagnostic selection.

†Further assessment may include thoracic radiography, echocardiography, blood pressure assessment, CBC, biochemistry, infectious disease testing, urinalysis, abdominal ultrasonography, and electrocardiogram.

Figure 4: Diagnostic algorithm describing the use of NT-proBNP to assess the likelihood of heart failure in dogs with respiratory clinical signs.

## Can the Cardiopet™ proBNP Test help with other clinical cases?

There are numerous other clinical scenarios in which measurement of NT-proBNP can help support clinical decision-making and patient care, including the following:

### NT-proBNP can be used to screen for dilated cardiomyopathy in some at-risk dog breeds

Doberman pinschers and Weimaraners with an NT-proBNP concentration above 500 pmol/L[15] and 405 pmol/L,[16] respectively, are at increased risk of heart disease and further evaluation with other diagnostic tests, such as an echocardiogram and Holter monitor, is advised. These thresholds are breed-specific and not generalizable to all dogs.

### Assessment of ascites in dogs

NT-proBNP can be used to help distinguish cardiac and noncardiac causes of nonhemorrhagic ascites. A study found that median NT-proBNP concentration in dogs with nonhemorrhagic ascites caused by cardiac disease (4,510 pmol/L) was higher than in dogs where the ascites was caused by noncardiac causes (739 pmol/L).[17] The two groups could be distinguished with a sensitivity of 54% and specificity of 86% when using a NT-proBNP concentration cut-off of 4,092 pmol/L.

### Assessing response to therapy and predicting long-term outcomes in dogs

In a study of 30 dogs with stage B2 MMVD, mean plasma NT-proBNP concentrations significantly decreased from 1,615 pmol/L to 959 pmol/L following 7–10 days of pimobendan treatment.[18] A study of 168 dogs with preclinical MMVD found that a NT-proBNP concentration > 1,500 pmol/L was associated with increased risk of heart failure or cardiac death.[19]

### Predicting severity of cardiac disease in cats

Median plasma NT-proBNP concentrations in mildly (216 pmol/L), moderately (283 pmol/L), and severely (840 pmol/L) affected HCM cats were significantly higher than healthy controls (18.9 pmol/L).[20]

### Assessing response to therapy and predicting long-term outcome in cats

In a study of 31 cats with Congestive Heart Failure (CHF), median serum NT-proBNP concentrations decreased significantly from admission (1,713 pmol/L) to discharge (902 pmol/L) and from admission to reevaluation in 7–10 days' time (1,124 pmol/L).[21] In a study of 25 cats with a cardiomyopathy and CHF, median serum concentrations of baseline NT-proBNP was significantly higher in the cats that died (> 1,500 pmol/L, n = 13) than in those that were alive (780 pmol/L, n = 12) at follow-up.[22]

## Are there any other factors that I need to consider when interpreting Cardiopet™ proBNP Test results?

### Renal function

NT-proBNP is cleared primarily by the kidney, and thus, significant renal insufficiency or prerenal azotemia may lead to increased concentrations. Therefore, NT-proBNP values should always be interpreted alongside biomarkers of renal function, such as SDMA, creatinine, and urine specific gravity.[23,24]

### Hyperthyroidism

Hyperthyroidism can cause secondary cardiac pathology in cats leading to increased NT-proBNP concentrations.[25,26] However, increased NT-proBNP concentrations in cats with hyperthyroidism should not be automatically assumed to be caused by elevated thyroxine concentrations since hyperthyroidism and a cardiomyopathy can occur as distinct, independent disease processes. Cats with hyperthyroidism and an increased NT-proBNP concentration should have their NT-proBNP concentration monitored following hyperthyroid treatment. Cats with a persistently increased NT-proBNP concentrations following a return to a euthyroid state should undergo further cardiac evaluation.

### Breed

Breed can influence NT-proBNP concentrations.[27,28] The interpretative guidelines are for a general canine population since breed-specific reference intervals have only been described for a small number of dog breeds. The breeds for which reference intervals have been reported include Chihuahuas (125–2,121 pmol/L),[29] Labrador retrievers (275–2,100 pmol/L),[30] and salukis (250–769 pmol/L).[31] Unlike dogs, breed has not been found to influence NT-proBNP concentrations in cats.[32]

### Individual variation

NT-proBNP concentrations can vary significantly in healthy dogs[30,33,34] and in dogs with cardiac disease.[34,35] Similarly, NT-proBNP concentrations can vary significantly in healthy cats.[36] Assessment of NT-proBNP concentrations when the patient has no or very early cardiac pathology can be helpful in assessing whether changes in NT-proBNP concentrations are clinically relevant for that patient. Dogs and cats with an increase of 60% in NT-proBNP concentration should undergo a more detailed reevaluation of their cardiac health.

## Contacting IDEXX: Expert feedback when you need it.

If you have any questions on when to use the Cardiopet™ proBNP Test or how to interpret test results, or if you would like treatment advice, please call for a consultation at 1-888-433-9987, option 4. IDEXX Telemedicine Consultants provides consultation and interpretation services for radiographic, ECG, and/or echocardiographic images. For more information, call 1-800-726-1212.

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