DEFINITION OF PRECLINICAL HCM

Hypertrophic cardiomyopathy (HCM) is a primary, genetic myocardial disease characterized by concentric ventricular hypertrophy, which may be symmetrical (diffuse) or segmental (localized) in distribution. Hypertrophy is often associated with changes in left ventricular (LV) diastolic function and in some cats, by progressive gross or microscopic changes in the left ventricular myocardium leading to ventricular systolic dysfunction. The morphological and functional abnormalities associated with HCM can be assessed using two-dimensional and Doppler echocardiography. Other causes of LV hypertrophy include systemic hypertension and thyrotoxicosis, but hypertrophy consequent to these diseases is considered a secondary form of cardiomyopathy rather than HCM. However, HCM, systemic hypertension and thyrotoxicosis are not mutually exclusive and may occur in the same patient. Potential consequences of HCM include congestive heart failure (CHF), arterial thromboembolism (ATE), syncope, and sudden cardiac death. These complications affect only a small percentage of cats with HCM, but it can be difficult to predict which cats are at highest risk for these outcomes.

Preclinical HCM is diagnosed when characteristic echocardiographic findings of HCM are documented in cats without clinical signs of heart disease. Systemic hypertension and thyrotoxicosis should be ruled out in age appropriate cats or in cats with evidence of concurrent disease. Auscultation findings are often, but not always, abnormal in cats with preclinical HCM. Regardless, abnormal auscultation findings do not confirm the diagnosis of HCM in the absence of echocardiographic examination.

Although the term “preclinical” is used here to indicate a lack of current or previous clinical signs attributable to heart disease, HCM is not predictably progressive. Some cats will never exhibit clinical signs of their HCM, or may show only transient clinical signs when challenged or stressed. Two common causes of cardiac decompensation in this disease are general anesthesia and fluid therapy.

ESTABLISHING A DIAGNOSIS

1. Breed risk (epidemiology): HCM is mainly a disease of middle-aged to older cats but can affect cats of all ages and all breeds, including mixed breeds. Breeds considered or suspected to have a higher incidence of HCM than the general feline population are presented in Table 1. Recently, genetic testing for HCM-related genetic markers has become available for Maine Coon and Ragdoll breeds.

2. Historical signs: Cats with preclinical HCM by definition have no outward clinical signs of the disease. However, subtle signs of cardiac disease (e.g. decreased activity, weight loss) may be interpreted by the owner as a “sign of aging” and not be recognized as a sign of heart disease. In some cases, preclinical status changes unexpectedly when CHF develops after fluid therapy, blood transfusion, surgery, or a period of stress.

3. Clinical findings: When detectable, common auscultatory abnormalities include a heart murmur, a gallop rhythm, an irregular heart rhythm, or any combination of these findings. Although these abnormalities may indicate the presence of heart disease, none is specific for HCM. Of these, gallop or irregular heart rhythms are most predictive of cardiac abnormality, while functional heart murmurs are heard in many cats without identifiable cardiac disease or occur secondary to a systemic problem (e.g. anemia). Recent studies suggest that at least 15-50% of random healthy cats have discernable heart murmurs while heart disease is identified in up to 50% of cats with murmurs following echocardiographic investigation. No particular auscultation finding is specific for HCM; any abnormality can be found in cats with any cardiomyopathy. In addition, the absence of auscultatory abnormalities does not preclude the presence of
HCM. Despite these inconsistencies, auscultation remains the primary method by which cats that may benefit from further testing can be identified.

Differential diagnoses for systolic heart murmurs in cats include various primary cardiomyopathies, LV hypertrophy secondary to thyrotoxicosis or hypertension (secondary cardiomyopathy), congenital heart disease, acquired valvular disease (very rare) and functional (physiologic) murmurs. Functional murmurs (murmurs occurring without identifiable anatomic cardiac abnormality) are more common in cats than dogs, and may be related to increased sympathetic drive (including stress), anemia, thyrotoxicosis, dynamic right ventricular outflow tract obstruction (DRVOTO), fever, or tachycardias associated with drugs such as ketamine. These differential diagnoses must be considered in cats with heart murmurs that have normal findings on echocardiographic examination.

**Table 1:** Breeds known or suspected of having a higher risk of HCM than the typical feline population.

<table>
<thead>
<tr>
<th>Breed</th>
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<tbody>
<tr>
<td>Maine Coon</td>
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<tr>
<td>American short-haired</td>
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<tr>
<td>Persian</td>
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<tr>
<td>Ragdoll cats</td>
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<tr>
<td>Sphynx</td>
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<td>British short-haired</td>
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<td>Norwegian forest cat</td>
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<td>Birman</td>
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<td>Himalayan</td>
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<td>Chartreux</td>
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<td>Bengal</td>
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**GENERAL INDICATIONS FOR AND INTERPRETATION OF DIAGNOSTIC TESTS**

**Cats with ausculted cardiac abnormalities with no clinical signs:**

Further cardiac investigation is recommended in clinically normal cats with ausculted cardiac abnormalities. This is especially important in breeding animals, cats in which anesthesia is anticipated, or in cats with vague clinical abnormalities that may or may not reflect heart disease. Diagnostic testing in an individual cat may include any combination of the following: echocardiography, NT-proBNP, blood pressure assessment, thyroid evaluation (if age appropriate), thoracic radiographs, electrocardiography (if an irregular heart rhythm is detected), and genetic testing (if breed-appropriate) (Figure 1). Identification of other systemic abnormalities present at the time of heart disease diagnosis may require additional biochemical testing, urinalysis, other imaging and additional examinations (e.g. fundic evaluation), as appropriate for the individual cat. In many cases, establishing “baseline” biochemical and urinalysis findings while the cat is without clinical signs is helpful as a comparison for future testing; this is especially true of baseline thoracic radiographs. The relative clinical importance of each of the suggested tests is considered below.

1. **Echocardiography:** Echocardiography is the gold standard for evaluation of overall cardiac size and specific cardiac chamber size, segmental wall thicknesses, and cardiac function. Cardiac ultrasound examination should be offered to clients whenever a murmur, gallop, or arrhythmia is identified. When performed by an experienced examiner, echocardiography establishes an exact cardiac diagnosis (e.g. DCM or congenital abnormalities), may provide clues reflecting systemic illness (e.g. left ventricular hypertrophy in the setting of systemic hypertension), reveal complications of myocardial disease (e.g. intracardiac thrombi), and may allow “fine-tuning” of the diagnosis in ways that may affect therapy (e.g. dynamic left ventricular outflow tract obstruction due to systolic anterior motion of the mitral valve [SAM]). Importantly, echocardiographic findings also may identify no cause or a benign cause – such as dynamic right ventricular outflow tract obstruction or idiopathic aortic dilatation – for an ausculted abnormality. In these cases, the echocardiographic examination can rule OUT serious heart disease, and decrease the concerns of both the clinician and the owner. Specific criteria for diagnosis and caveats regarding echocardiographic examination and interpretation appear later in this document under “Diagnosis of HCM by echocardiography”.

2. **NT-proBNP:** If echocardiography is declined, NT-proBNP testing may be used to provide information regarding the risk of cardiac abnormalities in an individual cat. Concentrations > 100 pmol/L increase the likelihood that heart disease is present, and the likelihood of disease increases further with higher NT-proBNP concentrations. Thus an elevated NT-proBNP concentration may be used to identify patients at higher risk of heart disease and thereby encourage an owner to pursue an echocardiogram for definitive diagnosis and staging.

3. **Blood pressure and thyroid evaluation:** Blood pressure can be measured via Doppler or oscillometric methods, and is an important component of evaluation of cats with a murmur, gallop, cardiomegaly, renal insufficiency, hyperthyroidism or known LV hypertrophy. If a patient is found to have LV hypertrophy by echocardiography, systemic hypertension must be ruled out as the cause of the hypertrophy, particularly in middle-aged to older cats. Similarly, serum thyroxine concentration should be evaluated in any age-appropriate (i.e. > 7 year old) feline patient with ausculted or echocardiographic abnormalities to exclude thyrotoxicosis as a cause of the detected abnormalities.

4. **Thoracic radiography:** Thoracic radiographs can be an important part of the diagnostic evaluation and are essential in evaluation of cats with respiratory signs. Even in cats without clinical signs, other thoracic abnormalities, cardiomegaly, or subclinical/mild congestive heart failure may be detected. Thoracic radiographs are normal in
some cats with HCM despite abnormal auscultation and echocardiographic findings. Thus radiographs should not be used to rule out feline HCM, but identification of cardiomegaly strongly supports a diagnosis of heart disease. When heart enlargement is evident, more frequent re-evaluations are indicated compared to the cat with normal cardiac size. Cardiomegaly can be diagnosed by subjective interpretation of radiographs, but calculation of a lateral vertebral heart size (VHS) is recommended. A VHS > 8.0 is consistent with cardiomegaly, but the presence of intrathoracic fat deposits may artificially increase the VHS in obese feline patients. Lastly, as suggested previously, cats with confirmed preclinical HCM are at risk for the development of CHF and baseline radiographs can improve the accuracy of diagnosis of CHF should clinical signs develop.

5. Electrocardiography: Electrocardiographic recordings (ECG) are the only method of evaluating cardiac arrhythmias, but are relatively insensitive for identifying cardiac enlargement. Therefore this test is inferior to other examinations as a “screening” test for HCM and is not recommended for this purpose. Findings that may be associated with HCM include tall R waves and left cranial axis shift patterns on the 6 lead ECG, but these findings are not specific for HCM. Currently, electrocardiography represents an ancillary study in most preclinical HCM cats but is remains highly recommended in any cat with an irregular heart rhythm.

PATIENTS AT RISK FOR BREED-RELATED HCM (SCREENING FOR BREED-RELATED HCM):
Echocardiography is the most efficient and frequently-used method of screening patients for HCM and is the gold standard for the diagnosis. However, findings can be confusing or ambiguous in young or mildly affected cats. The findings of HCM can be dynamic and change significantly over time: this point is relevant to both breeders and cat owners. Despite recent development in genetic testing for markers of HCM, negative tests do not rule out the disease and positive tests are not 100% predictive of clinical disease (see below). Other types of testing, including evaluation of biomarkers such as NT-proBNP, are discussed elsewhere on this site, and these biomarkers must be interpreted in the context of the population tested (for example, healthy versus symptomatic). Referral to a cardiologist is recommended for clients interested in pre-breeding screening for HCM in their cats.

DIAGNOSIS OF HCM BY ECHOCARDIOGRAPHY*
*Specific views and values for normality are not established. The values used here represent the consensus view of the CEG members.

1. Left ventricular findings:
The high degree of phenotypic variability in cats with HCM complicates diagnosis in mildly affected patients because of overlap of findings with those of normal cats. The core diagnosis is obtained by documentation of LV hypertrophy by 2-D or M-mode recordings. Two-dimensional examination is a necessary adjunct to M-mode measurements, because M-mode measurements may miss segmental hypertrophy, or over diagnose hypertrophy by inadvertent inclusion of papillary muscles in the recording. Systemic hydration status is an important consideration; dehydration or diuretic therapy may decrease blood volume and result in the appearance of LV hypertrophy in an otherwise normal heart (“pseudohypertrophy”). HCM may be diagnosed in cats with segmentally, asymmetrically or symmetrically thickened walls (maximal thickness of the interventricular septum [IVS] or left ventricular free wall [LVFW] in diastole). There is no universally accepted diastolic wall thickness considered to be both sensitive and specific for diagnosis of HCM, but most cardiologists consider LVFW or IVS thickness ≥ 6.0 mm in diastole to be abnormal.

No standard ranges are available to classify LV hypertrophy as mild, moderate or severe; thicker walls are generally thought to represent more severe disease but cannot be interpreted in isolation. The degree of left atrial (LA) enlargement provides additional information regarding the degree of ventricular dysfunction and may be the best indicator of current risk for thromboembolism or congestive heart failure (see below). The distribution of hypertrophy within the LV is highly variable and echocardiography reports that communicate only mean or single wall thickness measurements are inadequate to characterize the severity of HCM. Thus clinicians should expect echocardiographic reports that describe the presence and segmental distribution of hypertrophy, as well as assessment of papillary muscle size and morphology and LA size (see “Other Factors”, below). These details become important in patient management; for example, focal mid-septal or subaortic thickening is often benign and requires no therapy, whereas asymmetrical hypertrophy characterized by thickened LVFW and normal IVS is often associated with LA enlargement and indicates more severe disease.

Normal systemic blood pressure and thyroid status (cats ≥ 7 years) should be confirmed before a diagnosis of HCM is made. Other less common causes of LV hypertrophy include acromegaly and some congenital defects such as aortic stenosis or mitral valve dysplasia. Mitral valve dysplasia with
Two-dimensional echocardiographic examination can be used to measure LA size, to detect the presence of spontaneous echo contrast (“smoke”) or thrombi within the heart and to identify systolic anterior motion of the mitral valve (SAM). Doppler-echocardiographic examination is required to diagnose LVOT obstruction and mitral insufficiency, and to analyze LV segmental systolic function, diastolic function and LA contractile function; all are important concurrent findings or complications of HCM.

- **Left atrial size**: End systolic LA diameter can be measured using the right parasternal long axis view optimized for the left ventricular inflow tract (normal maximum diameter 16 mm). Alternatively, the 2-D right parasternal short axis view of the heart base can be used to measure the LA and Ao diameter and the LA:Ao ratio calculated to screen for LA enlargement (normal end-systolic 2D LA: Ao ratio: ≤ 1.5). Accurate timing of these measurements during the cardiac cycle (end systole) is important to acquire reproducible measurements (for example the first frame after the aortic valve closes or the frame prior to mitral valve opening). Although M-mode measurements based on the right parasternal short axis view of the heart base can demonstrate atrial dilation, these are not recommended for assessment of maximal LA size. An arbitrary “cut-off” between mild and moderate LA dilation as assessed in the right parasternal long axis view in an averaged size cat is approximately 20 mm (or LA:Ao > 2 in a right parasternal short axis view). Such assessments may be useful in deciding when to initiate antithrombotic therapy or to increase vigilance for development of congestive heart failure.

- **Presence or absence of echogenic smoke or thrombi**: Echogenic “swirling” resembling smoke may be noted within a moderately to severely enlarged left atrium and auricle and is thought to represent sluggish blood flow that can predispose to thrombus formation. In some cats a thrombus may be identified as a formed, homogenous echodensity attached to the wall of the LA or the left auricle. A thrombus can fill most of the auricle with the atrial surface either solid, or soft and moving freely within the cavity. Multiple image planes should be screened for intracavitary thrombi whenever LA enlargement is present, including right parasternal short and long axis views and left craniodorsal image planes directly adjacent to the left auricle.

- **Systolic anterior motion of the mitral valve (SAM)**: Dynamic systolic contact of the anterior mitral valve leaflet with the IVS, often leading to systolic outflow obstruction and mitral insufficiency, may be identified by M mode or 2-D echo. SAM likely develops due to abnormal papillary muscle positioning/function and anatomic abnormalities in the mitral apparatus; these have been identified in both cats and humans with HCM. SAM can be present without significant obstruction or LV hypertrophy, and also may be associated with other conditions, especially congenital mitral valve dysplasia.

- **LV outflow tract or mid-ventricular obstruction**: 2-D imaging (at high frame rates) may identify mid-ventricular obstruction or SAM, but confirmation of left ventricular outflow tract obstruction (LVOTO) or mitral insufficiency requires Doppler studies. The presence of SAM with Doppler evidence of obstruction (i.e. elevated trans-aortic systolic flow velocities) and mitral regurgitation (MR) is often considered to be an indication for beta blockade (e.g. atenolol). Septal hypertrophy may also contribute to left ventricular outflow tract obstruction.

- **Mitral regurgitation**: Mitral regurgitation (also called mitral insufficiency) may be present in cats with HCM due to papillary muscle distortion, valve annulus distortion, concurrent abnormalities of the mitral valve, or SAM. Moderate to severe MR may compound LA enlargement associated with HCM, and contribute to volume loading of the left ventricle increasing the risk of CHF. Differential diagnosis of mitral regurgitation in the cat includes other primary feline cardiomyopathies, LV hypertrophy in cats caused by systemic hypertension or thyrotoxicosis, or less often congenital dysplasia of the mitral valve.

- **LV systolic and diastolic function**: Global LV systolic function can be estimated by M-mode or 2D methods, but segmental systolic dysfunction may not be detected by these methods, especially in regions that have been infarcted or replaced with fibrous tissue but fall outside the M-mode region of interest. Tissue Doppler studies may be required to evaluate segmental systolic dysfunction in affected animals. Diastolic dysfunction is a hallmark of HCM and may be the predominant mechanism for heart failure. Assessment of diastolic dysfunction requires advanced Doppler evaluation (often including tissue Doppler studies) by an experienced echocardiographer.

- **Left atrial function**: Advanced Doppler methods can be used to identify and quantify LA dysfunction and these findings may be correlated to risk of thrombus formation. For example, left auricular velocities (emptying or filling) of <20 cm/sec are more likely to be associated with echogenic smoke (a precursor to thrombosis). Some medications such
as atenolol may depress LA function; this may be relevant in cats with moderate to severe LA dilatation.

**GENETIC TESTING FOR HCM IN PUREBRED CATS:**
A genetic test is available for the mutations linked to the development of HCM in Maine coon cats, and another test is available for Ragdoll cats (see http://www.cvm.ncsu.edu/vhc/csds/vcgl/cat-dna.html). Not all cats testing positive for the gene mutation(s) will develop an HCM phenotype, but both heterozygous and homozygous genotypes with the mutation confer a higher risk of HCM phenotype development for that cat and offspring. The identification of this genetic risk factor may lead to more frequent echocardiographic surveillance (q 6 months) for development of phenotypic HCM in affected cats. Most breeders are familiar with these tests and the interpretation of homozygous and heterozygous states, and while homozygous cats are usually removed from breeding programs, echocardiographically normal heterozygous cats are sometimes retained for breeding. Cats with normal test results are unlikely to develop HCM due to this specific mutation, but still may develop HCM related to other, as yet unknown, mutations or causes. Importantly, genetic testing cannot identify all mutations and cannot identify the phenotypic presence of HCM. Echocardiography remains the gold standard for diagnosis of the presence of phenotypic HCM, while genetic testing identifies a predisposition for development of mutation-related HCM.

**THERAPEUTIC RECOMMENDATIONS FOR ASYMPTOMATIC (PRE-CLINICAL) HCM PATIENTS**

*No large, multi-center, prospective studies are available regarding optimal therapy of HCM in preclinical or symptomatic cats. The following recommendations represent agreement among the members of the Cardiac Education Group.*

Recommendations for therapy of preclinical HCM patients are based on echocardiographic assessment of severity and theoretical risk of development of complications such as intracardiac thrombus formation, congestive heart failure and sudden death. Other diagnostic tests may be indicated as discussed above.

1. Ventricular findings consistent with HCM along with normal LA size or mild LA enlargement
   - If LVOTO (left ventricular outflow tract obstruction) is present (mid-ventricular or secondary to systolic anterior mitral valve motion [SAM] or septal hypertrophy): beta blockade is recommended (most often atenolol, 6.25-12.5 mg PO q 12 hrs).
     - Reduction of the severity of LVOTO is the target effect and is implied by a reduction in the intensity or absence of the heart murmur post therapy. Alternatively, actual measurements of LVOT velocities by Doppler echocardiography can be obtained. For practical purposes, the desired effects of beta blockers are more likely to be present when examination heart rate (HR) under provocation/stress is < 160 bpm. However, excessive reductions in HR (≤ 120 bpm in the hospital environment) is not recommended.
   - Gradual up-titration of dose is recommended until the goals of reduction of outflow obstruction or HR control is achieved.
   - Recent studies suggest that therapy with atenolol in cases of pre-clinical HCM or HCM with LVOTO does not prolong survival.
   - If LVOTO is not present: The value of any therapy is uncertain; the CEG recommends no therapy unless arrhythmias are also present; others have recommended atenolol or diltiazem empirically.
   - Arterial thromboembolism (ATE) prevention is not recommended at this stage of HCM.

2. Ventricular findings consistent with HCM with significant (moderate to severe) LA enlargement (previously defined)
   - ATE prevention is recommended:
     - Clopidogrel (Plavix®): 18.75 mg PO q 24 hrs, may be used with or without aspirin, and is the CEG’s preferred chronic antithrombotic therapy at this time.
     - Aspirin: When used as monotherapy or with clopidogrel, a dose of ¼ of an 81 mg tablet every third day (or twice per week) is usually well-tolerated, but the most effective dose of aspirin for this purpose remains uncertain.
   - Buprenorphine: for high risk patients (cats with previous thromboembolism, intracardiac thrombi or left atrial smoke), owners may be supplied with several syringes of buprenorphine to be administered orally at home if the cat develops sudden severe pain due to acute peripheral thromboembolism (approximately 0.045-0.06 mg/cat PO [0.15 to 0.2 ml of the 0.3 mg/ml concentration]).
   - Angiotensin-converting enzyme inhibitors (ACEI, enalapril or benazepril: 0.25-0.5 mg/kg PO q 12 – 24 h) are recommended by the CEG for use in cats with moderate-severe LA enlargement; proof of efficacy is lacking.
   - If concurrent LVOTO or mid-ventricular obstruction is present, a beta blocker (atenolol) is recommended with close observation and follow-up (as outlined above); beta blockers may depress atrial and ventricular function and theoretically increase the risk of congestive heart failure (CHF) or thrombus formation (ATE) in cats with moderate to severe LA enlargement.
   - If incipient heart failure is present (e.g. no pulmonary edema or pleural effusion, but marked LA dilation and vascular engorgement are noted on radiographs or echocardiogram; or if NT-proBNP > 300 pmol/L or serial NT-proBNP measurements have increased by > 100 pmol/L since last measured)
     - ACEI as above
Specific instructions for home resting respiratory rate monitoring are given. Resting respiratory rates less than 30 per minute indicate low risk of current/active CHF, whereas respiratory rates >35 should lead to prompt re-evaluation (see client handout elsewhere on the CEG website).

“Reserve” doses of furosemide may be prescribed for owners to give at home in case of acute tachypnea or dyspnea to decrease distress until hospital examination can be performed.

Use of beta blocker therapy in these patients should be approached with caution. Mild decreases in heart function caused by beta blockers may precipitate the onset of CHF in marginal (high risk) patients.

Avoid stressful situations in these cats (e.g. avoid elective anesthesia, boarding, stressful grooming situations etc.)

Avoid situations that may lead to increased plasma volume (e.g. intravenous fluid therapy, anesthesia, depot formulations of corticosteroids, etc).

CLIENT INFORMATION:

In cats with known heart disease but no clinical signs (preclinical stage), the information given to clients should center on providing basic, current information about the disease, preparing the clients for potential problems that may be anticipated with regard to elective procedures or anesthetic events and discussing which clinical signs they should watch for and what to do if they occur. This is a good time to introduce the concept of home monitoring of resting respiratory rate so that the client can identify a “typical” baseline respiratory rate for the patient (http://www.youtube.com/watch?v=uEptzj6G-Jk). This serves two purposes: to give the client a numerical scale to monitor the patient at home (with instructions on what to do if resting respiratory rate increases) and to provide the owner with a “sanity check” for use in case they think that they might be imagining increased breathing rate in their pet.

### Cat with Ausculted Abnormalities

- **No Clinical Signs Present**
  - Screen for systemic HT and thyrotoxicosis (if ≥ 7 years old)

- **Echo available**
  - Arrhythmia is present
  - ECG
  - Results normal
  - Results consistent with other heart disease
  - HCM or other heart disease not present at this time
  - Continue evaluation for staging of severity
  - Reinforce need for echo for definitive diagnosis

- **Echo not available**
  - NT-proBNP evaluation
  - Results ≥ 100 pmol/L (SNAP test +)
  - HCM or other heart disease may be present
  - Reinforce need for echo for definitive diagnosis

- **Results ≤ 100 pmol/L (SNAP test -)**
  - NT-proBNP evaluation
  - HCM or other heart disease not present at this time
  - Reinforce need for echo for definitive diagnosis

- **Results consistent with HCM**
  - Continue evaluation for staging of severity
  - Reinforce need for echo for definitive diagnosis

- **Results consistent with other heart disease**
  - Continue evaluation for staging of severity
  - Reinforce need for echo for definitive diagnosis

### Figure 1: Algorithm for evaluation of cats with ausculted abnormalities but no clinical signs. NOTE: If HCM or other heart disease is not identified in the current evaluation, the patient may develop these conditions in the future. Screening for hypertension and thyrotoxicosis is often performed before echocardiography when clinical suspicion of these abnormalities is high. ECG: electrocardiogram, Echo: echocardiogram, HCM: hypertrophic cardiomyopathy.