

Early Cancer Detection Tests: Do They Work?

We are all familiar with recommendations from physicians and other health advocacy groups for various kinds of cancer screening tests, such as mammograms to detect breast cancer, colonoscopies to detect and prevent colon cancer, Pap smears to detect and prevent cervical cancer, and PSA tests to detect prostate cancer. What all of these tests have in common is the theme that early detection saves lives. We also know that in people, cancers for which there are no good methods of early detection such as ovarian cancer and pancreatic cancer are often so advanced at the time of diagnosis that cure rates are low.

With that as context, it's completely understandable that we would be eager to embrace technologies that offer early cancer detection for our dogs. Our natural expectation is that the earlier cancer is diagnosed, the better chance our dogs will have for a cure or improved prognosis. And of course, this is especially on the minds of owners of breeds at highest risk for cancer¹.

Therefore, the recent announcement of a new cancer detection blood test² intended for use as “a wellness screen for the apparently healthy dog prior to the onset of visible signs” has raised a great deal of interest among dog owners. The most immediate question seems to be, “Does it really work?” While some of this discussion will be specific to this particular test, the general considerations can guide evaluation of other tests marketed for similar purposes.

Veterinary Diagnostic Institute's (VDI) INCaSe test uses measurements of thymidine kinase-1 (TK1) and C-reactive protein (CRP) in an undisclosed algorithmic formula to provide a result that is claimed to inform the owner with a high degree of accuracy that the dog is either at “increased risk for neoplasia or other disorder” (Positive); has a high probability of “active malignant disease” (High Positive); or at “low risk of major neoplastic disease in the next several months” (Negative). First we're going to discuss a little bit of the science behind this test (don't worry, just a few paragraphs!), and then we'll examine how “early cancer detection” screening as it currently stands impacts dogs and their owners.

Thymidine kinase-1 is an enzyme that is present in dividing cells, and since cancers by definition include uncontrolled cell division, it has long been known in humans that TK1 levels increase in the presence of cancer. The most dramatic rise is in hematologic (blood) malignancies, and the primary use for TK1 assays in humans is in monitoring remission in non-Hodgkin lymphoma. Note that it is *not* used as a screening test for early detection of disease in apparently healthy people, and we'll get back to that point in a minute.

A few small peer-reviewed (meeting accepted scientific standards) studies have validated that a rise in TK1 also occurs in dogs with lymphomaⁱ (LSA), and one recent study showed that TK1 rises in dogs with hemangiosarcomaⁱⁱ (HSA). All of these studies compared TK1 values in dogs

¹ However, although the risk is even higher in some breeds, 50% of all dogs over the age of 10 get cancer.

² INCaSe canine cancer screen (Initial Notification Cancer Screen), Veterinary Diagnostics Institute

with either LSA or HSA to normal dogs, and none of these studies included C-reactive protein testing (as does VDI's INCaSe test). CRP is a general measure of inflammation, and while it is not specific to cancer, elevated CRP has been associated with several kinds of cancer in people. Evidence is beginning to accumulate that CRP may also be elevated in dogs with several kinds of cancer^{iii iv}, but high CRP can also be caused by infection, some autoimmune diseases, and many chronic diseases. Likewise, TK1 can also rise for reasons other than cancer, such as viral infections and wound healing after trauma and surgery.

While some abstracts have been provided in the endnotes for those who want more details, what all of this means is that there is definitely some scientific support for the claim that TK1 and CRP levels are often elevated in dogs that have certain kinds of cancer, primarily lymphoma and hemangiosarcoma. What it does *not* mean, however, is that there is scientific evidence indicating that TK1 and CRP levels are elevated in “apparently healthy” dogs prior to the onset of other signs of cancer (a group that VDI targets for its INCaSe test). As of this writing (February 2012), there are no published peer-reviewed studies that have examined this question.

However, the study reported in Abstract *i* measured TK1 levels in dogs with lymphoma that had been treated with chemotherapy and were in remission. Investigators found that high TK1 levels at the time of diagnosis generally returned to normal during remission, and then rose significantly by three weeks prior to relapse. They concluded from this study that TK1 could be used to predict recurrence of disease several weeks prior to clinical signs, and this is very similar to the way that TK1 testing is used in monitoring people with non-Hodgkin lymphoma.

Although there are no peer-reviewed data to support this next supposition, for the sake of discussion let's just say that an “early cancer detection test” might be able to predict LSA or HSA in a healthy dog in advance of clinical signs. Or maybe some owners will just be interested in trying a test out of curiosity. So let's examine a couple of likely scenarios of what might happen if the result comes back “positive” on a well-dog screening test.

In the first scenario, the owner of course is worried and upset, and sets forth on a mission to find cancer. It is very likely that the owner will want further testing to be done, which may include ultrasounds, radiographs, blood panels, and maybe even an MRI. And at the end of all that, the owner has spent quite a bit of money and nothing was found. Without a specific disease to treat, the owner then just worries and waits for cancer to show itself clinically, and nothing useful was gained. A good case could be made that it would have been better not to have done a screening test, and instead of wasting resources chasing a diagnosis that wasn't yet detectable, wait until cancer becomes clinically evident (if it ever does – some results will be false positives). Those resources could then be spent on treating the dog if that is the owner's choice.

In an alternate scenario, prompted by a positive “early cancer detection test,” an abdominal ultrasound does indeed find a splenic mass. Although the test cannot tell for certain whether the mass is hemangiosarcoma or perhaps a benign hematoma, let's go with the worst case and say it's HSA and the dog has a splenectomy. Has anything been gained for dogs in which a tumor is discovered as a result of a positive screening test? Well, providing that the tumor is in an operable site, it's true that the dog will not suddenly collapse and die unexpectedly, and that is

certainly important to the very small percentage of owners whose dogs will fit this circumstance. Sadly, however, the deadly course of the disease will not have changed, because **early detection has never been shown to improve outcome with regard to ability to achieve remission, duration of remission, or overall survival time in either lymphoma or hemangiosarcoma.**

Further, if, for example, TK1 values can only predict disease a few weeks in advance of clinical signs (as research indicates to be the case in detecting lymphoma remissions) – and since HSA is an extremely rapidly developing disease -- there is probably only a very narrow slice of time in which the above scenario will apply. And indeed, VDI's own interpretation of a Negative result on their test states that the dog is at “low risk of major neoplastic disease in the next several months,” which appears to acknowledge that there is only a short window of time during which test results might be meaningful.

Reframing the Question

So where does this leave us? Unfortunately, for the vast majority of owners whose dog receives a positive result on an “early cancer detection test,” there will be nothing whatsoever that they can do to improve their dog's outcome based on having had the test. For this reason, some scientists who have developed other methods of early detection -- as well as many clinical general veterinarians and oncologists -- consider it questionable to promote or offer these kinds of cancer predictive tests. And let's come back to the case with humans, in which much more is known about TK1 testing. TK1 testing in humans is not used as a widespread or even targeted (to high-risk populations) screening test to predict lymphoma. Why? For the same reason -- it does not improve outcome.

In discussing a test marketed by another company (OncoPet Diagnostics, Inc.³) for the early detection of cancer in dogs, board certified veterinary oncologist Dr. Timothy Rocha noted in an online article, “It's made by a company that is out to make a profit so, of course, they want as many people to use their product as possible. The problem arises when people who love their pets feel the need to go on a ‘cancer hunt,’ subjecting their animals to a lot of unnecessary diagnostic testing that can actually stress your pet and cost owners thousands of dollars. Owners

³ OncoPet Diagnostic Inc Disclaimers, excerpted below, certainly raise some concern with this test also:

- The OncoPet RECAF™ test has **NOT** been approved by the U.S. Food and Drug Administration, the U.S. Department of Agriculture, or any other regulatory organization in any country for use in the diagnosis of cancer in any species
- Some normal animals may test positive for cancer (false positives) and some animals with cancer may test negative using the OncoPet RECAF™ test (false negatives). Depending on the type of cancer, the number of false negatives can be as high as 25% (75% sensitivity) and the number of false positives among normal dogs can be as high as 10% (90% specificity). It should be kept in mind that these figures are calculated from experiments done on the most common types of cancers in companion animals and therefore they may be different for other types of cancers for which sensitivity values might not have been assessed yet. Some acute inflammatory lesions produce very high levels of circulating RECAF™ and therefore samples from animals suspected of having an inflammatory process or infection should not be sent for testing.
- The calculation of the positive/negative cutoff value and the sensitivity and specificity of the test are estimated from a relatively small number of samples and might not reflect the values obtained from a larger number of samples

want to do what is best for their animals, but this type of testing doesn't always amount to a positive for your dog.”

Now, all that said, there may indeed be a more useful way to apply TK1 testing, and this is beginning to find its way into oncology practices. TK1 levels may be monitored during remission in dogs that have been treated with chemotherapy for lymphoma, following the model of a similar use in humans. Levels that remain high or become high during remission may indicate the need for more frequent follow-up intervals, so that rescue protocols can be initiated at the first sign of relapse. There is also some evidence to suggest that high TK1 levels prior to therapy correspond to significantly shorter survival time (Abstract *i*). However, for a number of reasons, it does not appear that this is currently in widespread use to predict response to therapy or duration of remission.

In summary, owners must decide for themselves and in consultation with their veterinarian whether any of the early cancer detection tests make sense for their dog in their individual circumstances. But as one considers the science behind and the value of tests marketed for the early detection of cancer, the initial question of “Does it really work?” should perhaps be reframed into the more relevant “Will it benefit my dog?”

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Abstracts

ⁱ [J Vet Intern Med.](#) 2004 Sep-Oct;18(5):696-702.

Serum thymidine kinase activity in dogs with malignant lymphoma: a potent marker for prognosis and monitoring the disease.

[von Euler H](#), [Einarsson R](#), [Olsson U](#), [Lagerstedt AS](#), [Eriksson S](#).

Source

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Abstract

Serum thymidine kinase (sTK) activity was evaluated as a tumor marker for canine malignant lymphoma (ML). The objective was to investigate if sTK, as in humans, could be used as a prognostic marker for survival time in dogs with ML and if sTK could identify early signs of progression of disease in treated dogs. Serum samples from 52 dogs with ML were tested for initial TK activity. Samples from 21 normal dogs and 25 dogs with nonhematologic neoplasms were used for comparison. Forty-four dogs with ML were treated. Serum TK activity was measured in treated dogs before each treatment and every 4 weeks thereafter until relapse. Dogs with ML had 2-180 times higher TK activity (TK 5-900 U/L) than normal dogs (TK <7 U/L) based on the mean + 2 standard deviations. In the group of other neoplasms, only 2 dogs had a moderate increase (6.4 and 7.5 U/L) compared with the controls. Mean sTK activities in the dogs with ML that had gone into complete remission (CR) were not significantly different from activities in healthy controls (P = .68). Mean sTK at least 3 weeks before and at the time of relapse was significantly higher than activity measured at CR (P < .0001). Dogs with ML that initially had sTK >30 U/L had significantly shorter survival times (P < .0001). Furthermore, sTK activity reflected the clinical staging of ML. Measuring sTK can be used as a powerful objective tumor marker for prognosis and for predicting relapse before recurrence of clinically detectable disease in dogs with ML undergoing chemotherapy.

ii [Vet Comp Oncol](#). 2011 Oct 20. doi: 10.1111/j.1476-5829.2011.00298.x. [Epub ahead of print]

Elevated serum thymidine kinase activity in canine splenic hemangiosarcoma(*).

[Thamm DH](#), [Kamstock DA](#), [Sharp CR](#), [Johnson SI](#), [Mazzaferro E](#), [Herold LV](#), [Barnes SM](#), [Winkler K](#), [Selting KA](#).

Source

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Abstract

Thymidine kinase 1 (TK1) is a soluble biomarker associated with DNA synthesis. This prospective study evaluated serum TK1 activity in dogs presenting with hemoabdomen and a splenic mass. An ELISA using azidothymidine as a substrate was used to evaluate TK1 activity. Sixty-two dogs with hemoabdomen and 15 normal controls were studied. Serum TK1 activity was significantly higher in dogs with hemangiosarcoma (HSA) than in normal dogs (mean \pm SEM = 17.0 \pm 5.0 and 2.01 \pm 0.6, respectively), but not dogs with benign disease (mean \pm SEM = 10.0 \pm 3.3). Using a cut-off of 6.55 U/L, TK activity demonstrated a sensitivity of 0.52, specificity of 0.93, positive predictive value of 0.94 and negative predictive value of 0.48 for distinguishing HSA versus normal. When interval thresholds of <1.55 and >7.95 U/L were used together, diagnostic utility was increased. Serum TK1 evaluation may help to discriminate between benign disease and HSA in dogs with hemoabdomen and a splenic mass.

iii [Vet Clin Pathol](#). 2009 Sep;38(3):348-52. Epub 2009 Apr 16.

Evaluation of serum haptoglobin and C-reactive protein in dogs with mammary tumors.

[Planellas M](#), [Bassols A](#), [Siracusa C](#), [Saco Y](#), [Giménez M](#), [Pato R](#), [Pastor J](#).

Source

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Abstract

BACKGROUND:

In veterinary medicine, there is increasing interest in measuring acute phase proteins as a tool in the diagnosis and monitoring of neoplastic diseases. Although mammary neoplasms are the most common type of cancer in dogs, acute phase proteins have not been extensively evaluated in dogs with mammary tumors.

OBJECTIVES:

The aim of this study was to evaluate serum haptoglobin (Hp) and C-reactive protein (CRP) concentrations in the dogs with mammary tumors and assess their potential association with malignancy.

METHODS:

A retrospective study of dogs with mammary tumors was performed. Serum concentrations of CRP and Hp were determined in healthy control dogs (n=20) and dogs with mammary tumors before surgery (n=41). Mammary tumors were grouped as carcinomas (n=24), fibrosarcoma (n=1), malignant mixed tumors (n=7), benign mixed tumors (n=6), and adenomas (n=3). CRP and Hp concentrations were compared in dogs with different tumor types and were also compared based on tumor size, lymph node infiltration, skin ulceration, fixation to underlying tissue, and time between tumor identification and removal.

RESULTS:

Hp concentration was significantly (P<.043) higher in dogs with mammary tumors (median 2.03 g/L, range 0.09-2.94 g/L) compared with controls (1.38 g/L, range 0.08-3.00 g/L), but the range of values overlapped considerably. CRP concentration was higher in dogs with carcinomas (4.70 mg/L, range 0.63-128.96 mg/L) vs controls (2.11 mg/L, range 0.25-6.57 mg/L) (P=.0008) and in dogs with ulcerated skin (14.8 mg/L, range 5.7-128.9 mg/L, n=3) compared with those without ulceration (2.4 mg/L, range 0.11-30.3 mg/L, n=38) (P=.048).

CONCLUSIONS:

Serum Hp and CRP do not appear to have value in diagnosing or predicting malignancy of mammary tumors in dogs. Higher CRP concentrations in dogs with mammary carcinoma suggest a role for inflammation in this tumor type.

^{iv} [Vet J](#). 2007 Jul;174(1):188-92. Epub 2006 Aug 9.

Changes in C-reactive protein and haptoglobin in dogs with lymphatic neoplasia.

[Mischke R](#), [Waterston M](#), [Eckersall PD](#).

Source

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Abstract

Acute phase proteins (APP) are regarded as a useful diagnostic tool in humans with lymphomas, leukaemias and multiple myeloma. C-reactive protein (CRP) and haptoglobin concentrations were measured in dogs with malignant multicentric (high grade) lymphoma (n=16), acute lymphoblastic leukaemia (ALL) (n=11), chronic lymphocytic leukaemia (CLL) (n=7) and multiple myeloma (n=8). Twenty-five healthy dogs served as controls. Measurements of the CRP plasma concentration were performed using a commercial ELISA and haptoglobin was measured with an assay based on its haemoglobin binding capacity. Global group comparisons using Kruskal-Wallis-test revealed significant group differences for both APPs ($P < 0.0001$). Median CRP concentrations were increased in all groups with neoplastic lymphatic disorders (lymphoma: 37.2mg/L, ALL: 47.8mg/L, CLL: 35.5mg/L, myeloma: 17.6mg/L) compared to controls (1.67mg/L; $P < 0.001$). Compared to the healthy controls (median=0.59g/L), haptoglobin was especially increased in dogs with ALL (6.8g/L, $P < 0.0001$) followed by dogs with malignant lymphoma (3.8g/L, $P < 0.0001$), CLL (3.2g/L, $P = 0.0008$), and multiple myeloma (3.0g/L, $P = 0.0163$). For both APPs, a wide range of values was found in all patient groups. The results indicate that particularly severe and acute lymphatic neoplasia, such as high grade lymphoma and ALL, cause significant acute phase reactions in dogs and must be included in the differential diagnoses of increased blood levels of these APPs.