Product Overview
2016
Welcome

Take control of your dog's health and get back precious time.

Dear dog lover and breeder,

As loving caretakers and companions to our four-legged best friends, we are committed to maintaining their health and well-being. Of course, we know that includes daily care including a healthy diet, exercise, teeth cleaning, nail trimming and regular visits to the veterinarian. But sometimes that is not enough and with advancing age comes new health concerns - like an increased risk of cancer.

Far too frequently, cancer is caught in its late stages, which often means less time to act. What if we could create effective and personalized cancer detection solutions that help maximize the duration and quality of life for our dogs?

At Sentinel Biomedical, our goal is to make this a reality.

One key part of the solution is early detection. It is estimated that this year at least 80,000 dogs will be diagnosed with cancer of the bladder/urinary tract/prostate (also known as TCC/UC). The cancer is generally a disease of mid-to-late life, with more than 95% of cases occurring in dogs age six years and older. Often a positive diagnosis comes after rounds of antibiotic and/or anti-inflammatory prescriptions to treat non-specific symptoms that may include: straining to urinate; repeated frequent attempts to urinate; blood in the urine; and recurrent bacterial infection. When repeated treatments for these symptoms fail to resolve them fully, the dog may then be evaluated for the presence of a tumor, usually via urine cytology, abdominal ultrasound, and/or cystoscopy. This incurs high costs and takes additional time, which allows for the mass to continue to grow and spread within the bladder and potentially beyond.

Detecting cancer earlier – before symptoms develop – gives you and your veterinarian more time to develop the best treatment strategy and may dramatically improve your dog’s outcome.

This product guide will explain more about our goals and vision at Sentinel Biomedical and our unique TCC/UC detection assay. This assay uses a non-invasive, urine-based test that can detect TCC/UC up to four months before clinical symptoms develop - giving you and your veterinarian precious time in which to act.

Dr. Matthew Breen, PhD, C. Biol, FRSB
Oscar J. Fletcher Distinguished Professor of Comparative Oncology Genetics
North Carolina State University College of Veterinary Medicine
Our Team

Sentinel Biomedical comprises an experienced team that is passionately committed to scientific innovation, focusing on exploring the molecular basis of canine cancers and the investigation of potential environmental influences that may be shared with human cancers.

Founded by a team of researchers at North Carolina State University College of Veterinary Medicine, Sentinel Biomedical is developing a series of rapid tests, under the Sentinel Biomedical CADET™ product line, to provide owners and veterinarians with access to reliable early CANcer DETection in dogs.

The CADET™ BRAF MUTATION DETECTION ASSAY is the first early detection system for canine TCC/UC, and is available exclusively through Sentinel Biomedical and the American Kennel Club.

Our dogs truly are our best friends, in the home and in the fight against cancer.
Early detection of cancer, before symptoms even present, may dramatically improve the prognosis and long-term survival of your best friend.

Cancer of the bladder/urinary tract/prostate in dogs is most commonly a form of transitional cell carcinoma (TCC), also known as urothelial carcinoma (UC). These malignant tumors can affect the bladder, urethra, and kidneys of male and female dogs and also the prostate of males. TCC/UC is generally a disease of mid-to-late life, with more than 95% of cases occurring in dogs age 6 years and older.

Canine TCC/UC is an aggressive form of cancer that often invades surrounding tissue and has a high metastatic potential.
Incidence Rates

While any breed is susceptible to developing TCC/UC, these breeds have higher than average incidence rates. When combined, these breeds account for over a third of all diagnosed TCC/UC cases in purebred dogs.

- American Eskimo Dog
- Australian Cattle Dog
- Australian Shepherd
- Beagle
- Bichon Frise
- Border Collie
- Parson Russell Terrier
- Lhasa Apso
- Rat Terrier
- Russell Terrier
- Scottish Terrier
- Shetland Sheepdog
- West Highland White Terrier
- Wire Fox Terrier
Typical TCC/UC diagnosis
This year more than 80,000 dogs will be diagnosed with TCC/UC – often in late stages, leading to lower survival rates.

A positive diagnosis typically comes after rounds of antibiotics and/or anti-inflammatory prescriptions to treat non-specific symptoms that may include straining to urinate; repeated frequent attempts to urinate; blood in the urine; and bacterial infection. When repeated treatments for these symptoms fail to resolve them fully, the dog may then be evaluated for the presence of a tumor, usually via urine cytology, abdominal ultrasound, and/or cystoscopy. All this incurs high costs and takes time, which allows for the mass to enlarge and potentially spread beyond the primary tumor site.

1. Dog shows non-specific symptoms: blood in urine/straining during urination. Antibiotics and/or anti-inflammatory medications administered.
2. Symptoms ease but the tumor continues to enlarge.
3. Antibiotics and/or anti-inflammatory medications administered for a second time. Again, symptoms ease but the tumor continues to enlarge.
4. Symptoms return and ultrasound and/or cystoscopy performed to detect the mass.

TCC/UC Diagnosis Cycle Over Time
Confirming Diagnosis

Currently the gold standard of TCC/UC diagnosis requires evaluation of a tumor biopsy. This invasive process brings risks associated with anesthesia and is both time intensive and costly. Not all clinics are equipped to perform this procedure and results may be inconclusive as tumor location can make it difficult to obtain sufficient amount of suitable tissue for comprehensive diagnosis.

Cost of Conventional Diagnosis

Conventional diagnosis is both time intensive and expensive:
- 3-4 clinic visits
- 2-3 rounds of antibiotic/anti-inflammatory medication
- Ultrasound(s)
- Precious time spent treating symptoms of the cancer rather than the cancer itself
Our Solution

BRAF MUTATION & CANINE TCC/UC

A single mutation in a gene called BRAF is present in 85% of confirmed canine TCC/UC cases.¹

This mutation is not found in the urine of healthy dogs or dogs that have nonmalignant bladder polyps, inflammation or cystitis.

It can be detected in cells shed in the urine of a dog well before symptoms of the disease develop, allowing for early intervention with the most appropriate treatment.

THE SCIENCE OF THE BRAF MUTATION

In 85% of canine TCC/UC, one nucleotide in the activation segment of the kinase domain of the BRAF gene changes from a T to an A, resulting in one amino acid change from valine to glutamic acid, producing a protein with increased activity.

Part of a family of proteins called RAF, the BRAF protein is an essential component in the healthy growth and normal function of cells. However, when there is a mutation in the gene that changes the BRAF protein, the cell machinery is disrupted. This causes the cells to proliferate abnormally, leading to tumor development.

HOW THE TEST WORKS

All dogs shed cells from their urogenital tract each time they pass urine.

The CADET™ BRAF MUTATION DETECTION ASSAY detects the presence of cells in the urine that are shed from a tumor and contain the mutated gene.

Detection of cells with a BRAF mutation is indicative that the dog has a TCC/UC.
Meet Sam

NEW TEST FOR EARLY DETECTION AND DIAGNOSIS OF CANINE TCC/UC SAVES PRECIOUS TIME

Sam had been a special dog since the day Deneen Thompson brought him home at age 8 weeks.

The adorable Beagle puppy proved to be loving, snuggly and clever. “He was very, very smart, right from the get-go. I personally did his training, and he just got everything quickly,” the New Jersey resident said.

Housetraining was no exception. Once he learned that the potty-area was outside, Sam never had another accident.

So when he started urinating in the house, Thompson was very worried. “I knew something was wrong,” she said.

Sam’s veterinarian suspected a urinary tract infection and prescribed antibiotics. Things got better, and then the accidents resumed. Another round of antibiotics was prescribed followed by the same routine of symptoms subsiding then returning. An X-ray showed no evidence of bladder stones. Finally, an ultrasound revealed a mass on Sam’s bladder wall. “We had not had a biopsy yet, but the veterinarian thought it was most likely cancer,” she said.

Thompson had heard about a new genetic test for canine TCC/UC, including bladder cancer - the CADET<sup>SM</sup> BRAF Mutation Detection test, which only required collecting a urine sample. She contacted the test’s creator, Dr. Matthew Breen, North Carolina State University Distinguished Professor of Comparative Oncology Genetics and co-founder of Sentinel Biomedical.

Soon, Thompson was outside, chasing Sam around the yard to collect some urine in a cup, and within a week she had the results. The results of the genetic test indicated Sam had a type of bladder cancer: Canine Transitional Cell Carcinoma/Urothelial Carcinoma (TCC/UC).

Sam underwent surgery to remove the tumor and part of his bladder, and a biopsy of the tumor confirmed that Sam had a TCC/UC of the bladder. Sam went through chemotherapy to fight the disease.

"Sam would have been gone a long time

Use of this test expedites time to diagnosis, leading to the best possible outcome for the dog

- Dr. Matthew Breen

After a couple of rounds of medications to treat non-specific symptoms, Sam Thompson (pictured left) was diagnosed quickly with TCC/UC by the non-invasive CADET<sup>SM</sup> BRAF Mutation Detection test.
before if we had not discovered this," Thompson said. “We hope we can help other dog owners have their ‘Sams’ a little longer too.”

The value of the CADET™ BRAF Mutation Detection Assay does not stop there. Breen’s laboratory continues to regularly monitor cancer cell reduction in detected TCC/UC cases, like Sam’s, to contribute to research into canine bladder cancer – a major focus of Breen’s work.

**Highest Level of Detection**
The CADET™ BRAF Mutation Detection Assay is the first early detection system for canine TCC/UC. A single mutation in the canine BRAF gene is present in 85 percent of confirmed TCC/UC cases. The CADET™ BRAF Mutation Detection Assay identifies tumor cells carrying this mutation in the urine of dogs with TCC/UC and is so sensitive that it can detect as few as 10 abnormal cells in a urine sample. This allows the cancer to be identified earlier than traditional methods.

With its forensic level of detection, the test can be used to reveal the presence of tumor cells up to 4 months before any clinical signs become evident. Owners of dogs with a detected BRAF mutation can follow up with their veterinarian and seek the most appropriate treatment very early in the course of the disease, which is expected to improve both the quality and duration of the dogs’ lives.

**Working with Breeders**
Breen and Sentinel Biomedical have teamed with the American Kennel Club (AKC) to offer a special screening test to owners on a subscription basis and involve them in the ongoing research into TCC/UC. Owners are encouraged to start screening their dogs from the age of 5 or 6, especially in high-risk breeds.

“The American Kennel Club is excited to team with Sentinel Biomedical to make this test available to our breeders and dog owners. We know it will improve the health of our dogs and give breeders valuable information,” said Mark Dunn, Vice President of AKC Registration & Development.

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**CONVENTIONAL DIAGNOSIS OF TCC/UC**

**PRESENTATION**
Many dogs first exhibit non-specific symptoms that are shared with other much more common non-malignant conditions: straining to urinate, frequent urination, and the presence of bacteria and/or blood in the urine.

**TREATMENT**
These dogs tend to be treated initially for non-specific symptoms, resulting in several cycles of antibiotics/anti-inflammatory medications, along with repeated urine culture, which can last several months - giving the tumor more time to grow and spread beyond original site.

**NEXT STEPS**
When these treatments fail to fully resolve the symptoms, the next steps are usually to perform urine cytology, abdominal ultrasound and/or cystoscopy. At that time a mass may be detected and biopsied leading to a positive diagnosis of TCC/UC.

**OUTCOME**
Once diagnosed, treatment for the cancer begins, but by then the cancer may have been growing for months and now be at an advanced stage. In some cases, by the time a diagnosis is made, the cancer has already spread to other parts of the body.

**THE CADET™ WAY**
The CADET™ BRAF Mutation Detection Assay allows owners to intervene earlier in this process, even before symptoms of TCC/UC become evident.
The National Beagle Club (NBC) is actively working with Breen in hopes of improving early detection of TCC/UC in the breed, said Darlene Stewart, chairperson of the NBC Health and Genetics Committee.

“NBC members supported Dr. Breen’s early research by sending in samples of tissue/urine from affected Beagles. Now a select group of volunteers across the nation has sent in urine samples from their older Beagles that are considered healthy, to continue the research. Even in the first group of 15 dogs, two had a detectable BRAF mutation in their urine. Both these dogs were subsequently shown to have a TCC/UC in their bladder even though no clear symptoms were present.”

**Annual Subscription**

An annual subscription to the CADET™ BRAF Mutation Detection Assay provides a service pack that allows owners to proactively screen their dog for the presence of a BRAF mutation three times over the course of the year. In the convenience of their home, owners collect urine from their dogs and ship to the Sentinel Biomedical laboratory once every four months. They receive the results back within two weeks and if the BRAF mutation is detected, the owner should schedule an appointment with their veterinarian as soon as possible for follow-up.

The tests are easy to use. Owners collect free-catch urine from their dog in a clean container, transfer to the collection pot provided with the service pack, seal it, and then ship the sample back. All packing materials and prepaid shipping labels are included with the subscription purchase.

“On detection of the BRAF mutation in urine, it is very important to follow up with a veterinarian to perform a thorough physical examination of the dog to confirm diagnosis and determine a treatment plan. Use of the screening test expedites time to diagnosis, leading to the best possible outcome for the dog,” Breen said.

The goal of early-detection screening is to give owners and veterinarians an opportunity to act earlier to fight the cancer.

“Our test is so sensitive that we are finding cases that show a positive result very early in the course of the disease, where a mass has not yet grown to sufficient size to be visible on ultrasound, well before it becomes symptomatic. We have seen it take at least 4 months before any mass is even evident on an ultrasound,” Breen said. “This is highly suggestive that we are catching the cancer early and is a great step forward.” Importantly, unlike other urine based tests, the CADET™ test is not affected by the presence of bacteria, blood or inflammatory cells in the urine, so even when a dog is symptomatic, the test can serve as a rapid indicator that a tumor is present.

**Breeder Pack**

Understanding a breeder’s desire to test their entire kennel, Sentinel Biomedical and the
American Kennel Club (AKC) have created a special Breeder Pack that offers a discounted rate when testing 3 or more dogs at once.

**Diagnosis/Monitoring Pack**  
The CADET® BRAF Mutation Detection Assay is also available direct to veterinarians for use in a clinical setting. Please visit www.sentinelbiomedical.com for more information.

**Join a National Study to Fight Canine TCC/UC**  
Included with each service pack is a questionnaire that owners submit with each sample. The questionnaire will be used as part of a nationwide study aimed at finding the cause of TCC/UC and determining any link between genetic and environmental factors. Questions cover topics such as the major source of drinking water for your dog; if lawn care products are used on your yard; and if your dog is exposed to second-hand tobacco smoke.

Breen performs geographic mapping of TCC/UC cases in the high-risk breeds, and when he sees a cluster of affected dogs in a certain area of the country, the team investigates if there might be a common environmental concern in that area. He then references litter mates of these dogs in other areas of the country to see if they have developed any signs.

“Part of the goal for our offering this test is to work with breeders and owners to gather more data about how long it takes for a canine TCC/UC to develop, and which factors may contribute to their development,” Breen said.

"Sam would have been gone a long time before if we had not discovered this."

- Deneen Thompson  
Sam’s owner
### Test Benefits

**FORENSIC LEVEL DETECTION**

The CADET℠ BRAF MUTATION DETECTION ASSAY is the most sensitive means to detect the presence of a canine TCC/UC, up to 4 months (and possibly longer) before any signs of clinical disease become evident in a dog.

This allows treatment for the cancer to begin sooner rather than waiting for repeated use of antibiotic/anti-inflammatory medications. Early detection allows an owner to direct resources to treat disease rather than symptoms, and saves precious time.

**Accessible**
- Non-invasive
- Can be performed conveniently at home
- Easily submit samples to the testing laboratory with a simple free-catch urine test

**Affordable**
- Reduce fees associated with repeated clinic visits
- Avoid costs associated with treating non-specific symptoms

**Reliable**
- Forensic-level detection: the CADET℠ BRAF Mutation Detection Assay can detect TCC/UC with as few as ten mutation-bearing cells in the urine sample

**Time Saving**
- Results in 2 weeks
- Detect TCC/UC up to 4 months (and possibly longer) prior to clinical symptoms
- Provides more time to optimize treatment strategies

**Benefits all dogs**
- When you test your dog(s), you will be part of a nationwide study, helping our research team investigate the genetic and environmental factors associated with TCC/UC. In return, we will send you updates on our research.
- Program participation not only helps your dog but also helps better understand TCC/UC in your breed and in all dogs.

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**BE AN ADVOCATE FOR ALL DOGS**

Experienced and dedicated owners and breeders are knowledgeable about cutting-edge canine health research. As educated ambassadors, we encourage you to spread the word about this new test to your community, fellow breeders, dog owners and veterinarians. To request additional educational material, email us at info@sentinelbiomedical.com
Our Products

Annual Subscription

$299.00 (regular price $429)

Your annual subscription provides all the information and supplies you need to collect and submit three urine samples (3 tests in one year) from a single dog for BRAF mutation testing by Sentinel Biomedical:

- Detailed instructions
- Three (3) individual service packs, each containing a sample submission form, urine collection pot, and a prepaid FedEx return shipping label
- A magnet to remind you when to send each sample for testing

Diagnostic Pack

To purchase for veterinary clinics, please visit: www.sentinelbiomedical.com to order directly from Sentinel Biomedical.

Breeder Pack*

Test all the dogs in one household at one time for a reduced rate:

- 3 Pack - $299 ($100/test)
- 4 Pack - $360 ($90/test)
- 5 Pack - $405 ($81/test)
- 6 Pack - $438 ($73/test)

BREEDER PACK includes:

All materials to collect and package urine samples, sent directly to your door.

- FREE shipping to send all samples back to the laboratory for testing
- Rapid results in just two weeks from receipt of urine sample

* Breeder Pack includes a single test for each dog in a household. All samples purchased in a single Breeder Pack must be shipped together at one time to the Sentinel Biomedical laboratory.
DETECT the presence of TCC/UC up to 4 months (and possibly longer) before any signs of clinical disease become evident. This allows for identification of the disease in its earliest stages.

DIAGNOSE TCC/UC quickly. This will allow treatment for the cancer to begin sooner without the delay associated with treating non-specific symptoms.

MONITOR the effectiveness of treatment. If the cancer responds to a treatment, the number of cancer cells shed into the urine reduces. The assay may help to determine if the cancer returns after initial therapy, allowing alternative treatment options to be considered.