IDEXX DecisionIQ™

Addison's disease risk indication

The Addison's Disease Risk Indication feature offered through IDEXX DecisionIQ™ provides visibility into dogs who are at increased risk compared to other dogs of a current diagnosis of hypoadrenocorticism (Addison's disease) based on an ACTH stimulation test.

Collaborative human–machine teams, veterinarians, and artificial intelligence (AI) systems can actively enhance each other's complementary strengths.[1]

Artificial intelligence (AI) is a rapidly growing technology sector worldwide, and expansion into the medical realm is increasing in both human and veterinary medicine. Some examples of AI that exist within the medical field include speech recognition software to integrate medical record information, imaging modalities, digital wearable technologies, and decision support tools.[2]

The goal of AI in veterinary medicine is to improve efficiency in practice, patient health outcomes, and patient quality of life.[2,3] One form of AI, machine learning, analyzes millions of datapoint combinations by assessing patterns to generate relevant, patient-specific insights. This process can create new insights into diseases, providing veterinarians with additional information that, when combined with their own insights into the patient's clinical picture, enables them to diagnose and treat patients earlier and more effectively.[2,3]

Predictive modeling provides an opportunity to identify dogs at increased risk of Addison's disease in the early preclinical stage of disease and prior to electrolyte changes.

The success of machine learning is created through the development of complex algorithms, strenuous model assessments, and significant testing within the technological development phases. One important output of this rigorous development process is the ability of the AI system to learn how to analyze complex datasets. Through data analysis, AI models can help veterinarians identify diseases not only in late-stage disease, but also in the early or preclinical stages. This is exactly what the IDEXX DecisionIQ™ Addison's Disease Risk machine learning AI model provides: insights into dogs that currently have an increased likelihood of testing positive for hypoadrenocorticism (Addison's disease).

Clinical signs of Addison's disease may range from intermittent subtle or nonspecific signs to acute hypovolemic shock.

Hypoadrenocorticism (Addison's disease) is an uncommon, yet serious condition in dogs who have deficiencies in adrenal hormones (i.e., cortisol, aldosterone). In primary Addison's disease, adrenal hormone deficiency is due to destruction (primarily immune-mediated) of the adrenal cortices. Decreased cortisol that results from the destruction of the zona fasciculata and zona reticularis is the most consistent finding in Addison's disease.[4] This glucocorticoid deficiency inhibits a patient's ability to respond to internal and external stress appropriately. Clinical signs of cortisol deficiency include lethargy, inappetence, and in some cases, chronic or intermittent vomiting and/or diarrhea. These signs may manifest more strongly following stressful events.

In the majority of dogs with primary Addison's disease, the zona glomerulosa is also affected, resulting in mineralocorticoid deficiency as well. Mineralocorticoid deficiency leads to electrolyte disturbances, including change to increased potassium and decreased sodium. Addison's disease patients with significant electrolyte abnormalities may present acutely with hypovolemia and shock. The "typical" form of primary Addison's disease includes both glucocorticoid and mineralocorticoid deficiencies.[5]

25%–30% of Addison's patients have normal electrolytes at diagnosis.[4]

An "atypical" form of Addison's disease has been described in which there are normal electrolytes, suggesting a deficiency of glucocorticoids with normal mineralocorticoid levels.[5] Studies suggest that 25%–30% of Addison's disease patients have normal electrolytes at diagnosis.[4] Absent the classic electrolyte changes, laboratory findings may be subtle (e.g., lack of a stress leukogram) or similar to those seen in other more common conditions (e.g., decreases in albumin and cholesterol suggestive of gastrointestinal or liver disease).

Many "atypical" cases go on to develop electrolyte abnormalities in the future.[6–7]

Historically, atypical Addison's disease was theorized to be due to a sparing of the zona glomerulosa layer, with destruction of only the outermost layers of the adrenal cortex. Although this has been documented to occur, 6 recent studies have demonstrated that many of these "atypical" cases actually do have deficiencies in aldosterone, in which the body is compensating through other mechanisms and will go on to develop electrolyte abnormalities in the future.[6,7]

Secondary hypoadrenocorticism, which is also accompanied by normal electrolytes, results when endogenous ACTH production by the pituitary gland is suppressed. This may occur spontaneously due to a pituitary gland lesion or congenital defect (rare). More commonly this occurs secondary to iatrogenic steroid administration, especially following rapid withdrawal.[4]

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Addison's disease is sometimes referred to as the "great pretender" due to the variability of clinical signs, laboratory results, and patient history. Dogs with Addison's disease may present with nonspecific clinical signs that wax and wane over months to years, or they may present in an acute hypovolemic shock crisis. Laboratory abnormalities may mimic changes seen in other diseases, such as decreased liver function, gastrointestinal disease, and acute kidney injury, or may be very subtle and nonspecific. If a patient is exhibiting nonspecific signs over a long period of time, a veterinarian may utilize a great deal of time and resources while trying to treat the variety of clinical presentations that a patient may be exhibiting. In other cases, subtle clinical signs may even go unrecognized until a stressful event (e.g., routine dentistry) triggers an acute crisis. In acute cases, or if a patient remains undiagnosed, the condition is life-threatening.

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Early detection of Addison's disease is challenging because these patients may not have any clear indication of disease on preliminary laboratory testing. The ability to detect Addison's disease prior to the development of an Addisonian crisis would provide an opportunity to institute lifesaving treatment before the patient becomes critically ill.

The IDEXX DecisionIQ™ Addison's Disease Risk Indication feature utilizes AI technology to assess patient-specific results, allowing early detection and intervention in both preclinical and clinical disease phases, with or without electrolyte changes. The Addison's Disease Risk Indication feature is not intended to diagnose hypoadrenocorticism, but instead, it increases recognition of dogs who are at an increased risk of having Addison's disease compared to other dogs, and for whom screening for Addison's disease may be appropriate.

The Addison's Disease Risk Indication feature is a supervised machine-learning AI model.

Overview

The Addison's Disease Risk Indication feature was built using a **supervised** machine-learning method. The supervised method involves utilizing very large sets of anonymized patient data to provide a labeled training set of defined positive cases (patients who have the attribute of interest) and negative cases (patients without that attribute).[3]

Set criteria for inclusion or exclusion in the datasets, as well as the definition of positive, are predetermined by human medical experts. The machine, presented with the training set, looks backwards at patient results in the months prior to the diagnosis. From this data, the machine uses mathematical algorithms to learn the patterns and relationships of weighted analytes and trends, along with other patient data, such as signalment, until it finds the model that best predicts the eventual diagnosis. Once the model is defined, it goes through a preclinical technical validation for performance requirements on labeled data followed by a clinical evaluation in the field on unlabeled patient results.

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Algorithm development

A large database of results performed either at IDEXX Reference Laboratories or in-clinic on IDEXX analyzers, combined with clinical history data derived from integrated veterinary clinic practice information management systems (PIMS), was used to train the model to predict ACTH stimulation test results consistent with Addison's disease. The database included results from over 160 million canine patients that represented over 60,000 veterinary clinics across the United States. A wide dog population with diverse clinical presentations was included in the training dataset to give the model a more realistic representation of the general patient population. Because of the goal to detect early or preclinical cases in addition to more classic presentations, cases were not restricted to those with clinical signs or to dogs in which Addison's disease was already suspected.

To develop the training dataset, medical experts created a canine Addison's disease phenotype to define and label positive cases (i.e., canines with Addison's disease) and negative cases (i.e., canines without Addison's disease). The phenotype involves many inclusion and exclusion criteria to define cases as positive or not. Briefly, positive cases were adult dogs with an ACTH stimulation test consistent with hypoadrenocorticism (pre- and post-ACTH stimulation cortisol results < 2 µg/dL [55 nmol/L]), without recent systemic or topical glucocorticoid treatment, and with no history of prior diagnosis of or treatment for Cushing's disease. Dogs < 1 year old or > 15 years old were excluded.

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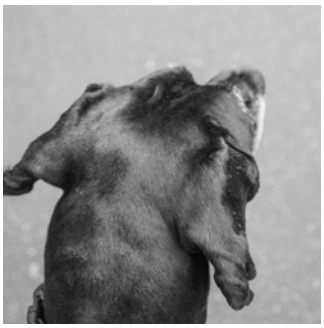
Addisonian dogs with and without electrolyte abnormalities were included to enable the ensemble machine learning model to be able to identify both typical and atypical or early Addison's disease cases. A subset of the cases was set aside for later use as a testing set for validation of the model's technical performance and were not included in the training set.

Data from the 30 days prior to the positive ACTH stimulation test for positive dogs or from the most recent 30 days for negative dogs was used to train the model. VetConnect® PLUS and PIMS data used to train the model included common blood work results, such as complete blood count (CBC) and serum chemistries (e.g., blood urea nitrogen [BUN], sodium, and potassium) as well as demographic data like gender, breed, and age. The minimum requirements for the model were commonly assessed parameters as found in CBC and chem 10 with electrolytes. For enhanced detection of atypical or early Addison's disease dogs, a chem 17 or larger chemistry panel is recommended due to the inclusion of other helpful analytes, such as cholesterol. The model parameters were optimized to meet predetermined performance criteria of specificity of ≥ 95% with sensitivity of at least 50%.



The model was taken through both a preclinical technical validation and a clinical medical evaluation.

Technical and clinical evaluation

The Addison's Disease Risk Indication model that was developed using the training set was then taken through several validation stages. The first is a preclinical technical validation to confirm that the model meets the performance requirements, assess for bias, and determine whether the model is strong enough to support a prospective clinical evaluation. The preclinical technical validation was performed by running the model against the labeled testing set of retrospective cases that had been held out for that purpose. Biostatisticians reviewed the model output to calculate the sensitivity and specificity for the model's ability to predict which cases would go on to have a positive ACTH stimulation test result for Addison's disease versus those that would not have a positive ACTH stimulation test. The results were also assessed for bias within important patient subgroups, such as different breeds and ages, to ensure consistent, unbiased performance.

For the prospective clinical medical validation, the Addison's Disease Risk Indication model was deployed for 222 participating veterinary practices in the United States and Canada for a period of four months. The model was run on all canine patients from those clinics that had results for a minimum set of laboratory analytes relevant to the model. Positive predictions were provided to veterinarians alongside their VetConnect® PLUS results with recommendations for next steps incorporating veterinarian-provided input on clinical signs and medication history.

Only the veterinarian, with their deeper insights into each specific patient, can diagnose hypoadreno-corticism.

A positive prediction should be interpreted to mean that the dog is at an increased risk of having Addison's disease, and the recommendation is to consider a resting cortisol to screen for Addison's disease, followed by, if indicated, an ACTH stimulation test to confirm a diagnosis of Addison's disease. Clinical expert validation was performed by a veterinarian board certified in internal medicine to determine the accuracy of the model. The blood work associated with the positive predictions (exclusive of any follow-up cortisol testing) and clinical history were reviewed, and each case was scored as positive (Addison's disease should be included as a differential diagnosis and should be screened for) or negative (Addison's disease is unlikely in this case).

Although the Addison's Disease Risk Indication model is not intended to diagnose Addison's disease, the results of follow-up diagnostic testing for Addison's disease can provide additional information about the clinical value of a positive prediction. Follow-up testing by veterinarians included either a resting cortisol followed by an ACTH stimulation test if indicated or in some cases where suspicion was high, only an ACTH stimulation test was performed.

Preclinical technical validation

The model demonstrated excellent performance when run against the testing set of negative and laboratory-confirmed positive cases. The model showed a specificity of 98% and sensitivity of 83% (table 1), exceeding the performance requirements for a high specificity of ≥ 95% with sensitivity ≥ 50%.[8]

Table 1.
Sensitivity and specificity on the Addison's Disease Risk Indication model when tested against the retrospective testing set.

	Sensitivity	Specificity
Preclinical technical validation	83%	98%

Clinical medical validation

During the 4-month period of the prospective clinical medical validation, a total of 54,500 patients were evaluated by the model. Of these, only 109 (0.2%) of the dogs received a positive prediction, consistent with the low prevalence of Addison's disease. Clinical expert validation was performed on these 109 cases by a veterinarian board certified in internal medicine. Agreement with the model on positive predictions was defined as a case for which the specialist would have included Addison's disease on the differential list for a sick patient with consistent clinical signs. In the case of patients who appeared clinically healthy, agreement was based on whether the specialist would have recommended ruling out Addison's disease with a resting cortisol prior to performing an elective procedure (e.g., dentistry) due to the risk of inducing a crisis event in an untreated Addisonian dog. The agreement of the model to the expert opinion that Addison's disease should be creened for revealed an accuracy for positive predictions of 74.3%.

Table 2.
Model accuracy of positive predictions based on agreement with expert medical opinion following review of cases with positive prediction.

	Total positive predictions	Expert review = consider Addison's disease	Accuracy
Clinical medical validation	109	81	74.3%

Laboratory confirmation of Addison's disease

When an increased likelihood of Addison's disease is detected, a resting cortisol is recommended as an initial screening test, followed by an ACTH stimulation test if indicated. A resting cortisol result of > 2.0 µg/dL (55 nmol/L) can be used to exclude Addison's disease.[9–11] Of the 109 dogs that received a positive disease risk indicator, follow-up cortisol testing (resting cortisol, ACTH stimulation test, or both) was performed on 41 dogs (37.6%). A resting cortisol test was performed on 28 (68.2%) of these dogs, with a result of < 2.0 µg/dL in 20 (71.4%) dogs. An ACTH stimulation test was performed in 9 of the 20 dogs with a low resting cortisol and had results (pre- and post-cortisol ≤ 0.5 µg/dL (28 nmol/L) consistent with Addison's disease in 6 dogs (66.7%). For 13 dogs (31.7%), the veterinarian did not screen with a resting cortisol but instead performed an ACTH stimulation test as the initial test. In 9 (69.2%) of these 13 dogs, the ACTH stimulation test results were consistent with Addison's disease.

Table 3.
Results of follow-up testing performed to assess for Addison's disease following a positive prediction. Total number of dogs receiving a positive prediction N = 109.

	Number of dogs with follow-up testing	Resting cortisol < 2.0 µg/dL (55 nmol/L)	Both pre- and post-ACTH cortisol ≤ 0.5 µg/dL (28 nmol/L)
Resting cortisol with or without ACTH stimulation test	28/109 (25.7%)	20/28 (71.4%)	6/9 (66.7%)
ACTH stimulation test only	13/109 (11.9%)	n/a	9/13 (69.2%)
Total	41/109 (37.6%)	20/28 (71.4%)	15/22 (68%)

The goal of the Addison's Disease Risk Indication feature is not to replace diagnostic testing for Addison's disease, but it is to bring awareness to those dogs for which Addison's disease should be considered as a differential diagnosis. Addison's

When an increased likelihood of Addison's disease is detected, a resting cortisol is recommended as an initial screening test.

disease is a rare condition with reported prevalences ranging from 0.06 to 0.28% in the general patient population,[12–15] rising to 4% amongst patients with chronic gastrointestinal signs.[14] Because of the low prevalence of Addison's disease, not all positive predictions will result in an end-diagnosis of Addison's disease.

For this reason, a resting cortisol is recommended as an initial screening test prior to pursuing more expensive ACTH stimulation testing. These early results demonstrate the value in screening with a resting cortisol when an increased likelihood of Addison's disease is detected.

Approximately 30% of the time, Addison's disease is not diagnosed until after an Addisonian crisis.[17]

Addison's disease is a very rare, but potentially fatal, disease that can be easily missed, particularly in the early stages of disease or when electrolytes are normal. Prior to an Addisonian crisis, the clinical signs and laboratory findings mimic other more common diseases, such as primary gastrointestinal disease, liver failure, or renal disease. In the early stages of the disease, dogs may have very subtle signs or may appear clinically healthy. Even at this early stage, a stressful event, such as an elective surgical procedure, can result in a crisis. Addison's disease may also occur concurrent with other more common endocrine diseases, such as hypothyroidism and diabetes mellitus.[16] The mixed laboratory changes in multi-endocrine cases can make identification of Addison's disease more difficult. Approximately 30% of the time, Addison's disease is not diagnosed until after the dog has experienced an Addisonian crisis.[17] These crises can be severe, often requiring hospitalization. Left untreated or without rapid intervention, Addison's disease can be fatal.

Increased recognition of dogs at risk for Addison's disease has the potential to enable earlier detection and treatment, prior to the onset of severe, life-threatening complications.

The IDEXX DecisionIQ™ Addison's Disease Risk Indication feature utilizes a machine-learning model to analyze patient signalment and laboratory data to identify dogs with an increased likelihood of testing positive for Addison's disease. In these dogs, particularly if consistent clinical signs are present, screening with a resting cortisol is recommended. In clinically healthy patients scheduled for routine surgical procedures, detection of an increased risk of preclinical Addison's disease on routine preanesthetic blood work provides an opportunity to rule out Addison's disease with a resting cortisol prior to anesthesia. Increased recognition of dogs at risk for Addison's disease has the potential to enable earlier detection and treatment, prior to the onset of severe, life-threatening complications.

Read how the IDEXX DecisionIQ™ Addison's Disease Risk Indication feature added value in two very different patient presentations:

Toby: A hypoadrenocorticism (Addison's disease) case study—early detection during a preanesthetic workup in an apparently nonclinical dog.

Bandit: A hypoadrenocorticism (Addison's disease) case study—detection in a sick dog initially suspected of a foreign body.

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