Cushing's syndrome:
Update on diagnosis and treatment.

Bill Saxon, DVM, DACVIM, DACVECC

IDEXX Medical Education Specialist

Dechra

IDEXX

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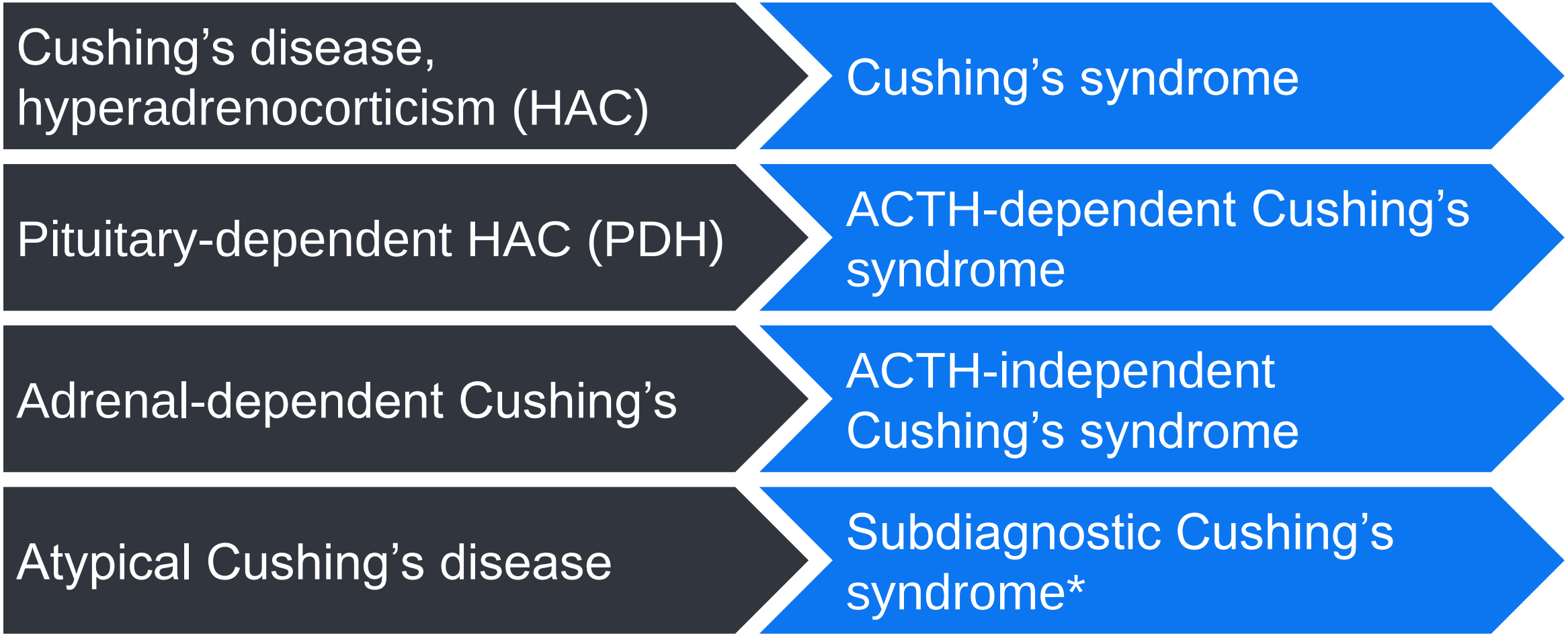
Disclosure:

Bill Saxon is a full-time employee of IDEXX.

The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical exam and presentation, and laboratory data. With respect to any drug therapy or monitoring program, you should refer to applicable product insert(s) for complete description of dosage, indications, interactions, and cautions. Diagnosis, treatment, and monitoring should be patient specific and is the responsibility of the veterinarian providing primary care. (2025)

ALIVE: Agreeing Language In Veterinary Endocrinology

Cushing’s then and now…



*Can be ACTH-dependent or ACTH-independent

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What’s the best way to diagnose Cushing’s syndrome?

Right patient, LDDST, abdominal ultrasound.

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Cushing's *syndrome* for a reason. Test only dogs/cats with:

- *Multiple* clinical signs of disease.
  - Cats skin hyper fragility, folded ear tips, no pu/pd unless also diabetes mellitus
- *Multiple* laboratory abnormalities consistent with Cushing's syndrome.
  - **Cats do not have increase ALP**, usually just hyperglycemia (if diabetes mellitus)
  - **ALT > ALP more likely primary liver disease**
- No other underlying disease (or with a controlled underlying disease).
- Have not received glucocorticoids (topical, oral, or injectable)
  - Unless suspect iatrogenic Cushing's syndrome

Testing the wrong patient patients leads to more false-positive results.

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Why LDDST to screen?

A good screening test has high sensitivity (minimize false negatives)

	Sensitivity	Specificity
UCCR	99%	25%
LDDST	95%	71%
ACTH Stim	60-80%	90%

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LDDST: *Screening* Interpretation

0.01 mg/kg IV dexamethasone IV. 0, 4, 8-hr cortisol.

1. Look at 8 hr cortisol result (ignore 4 hr for now)

   IF cortisol >1.4 µg/dL (use your lab's cut-offs)

   Consistent w/ Cushing's syndrome

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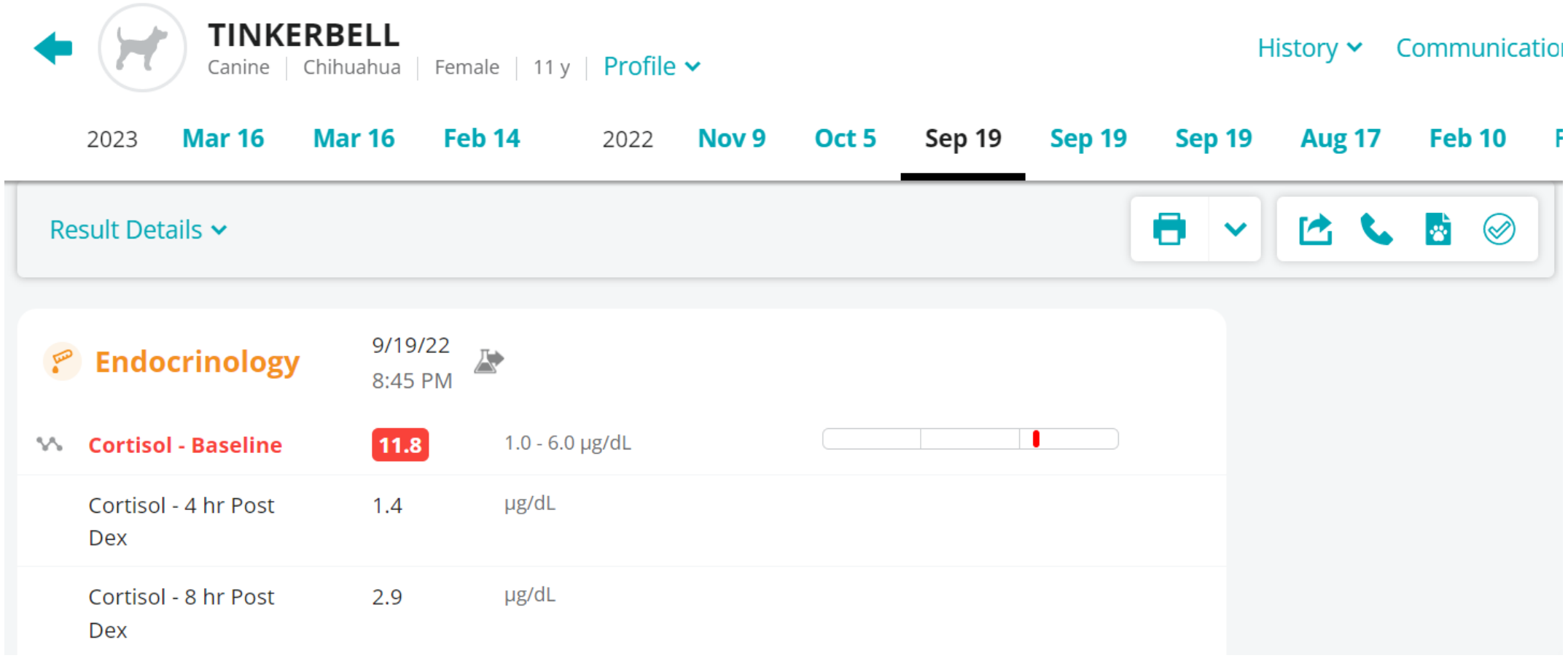
Cushing’s syndrome or not?



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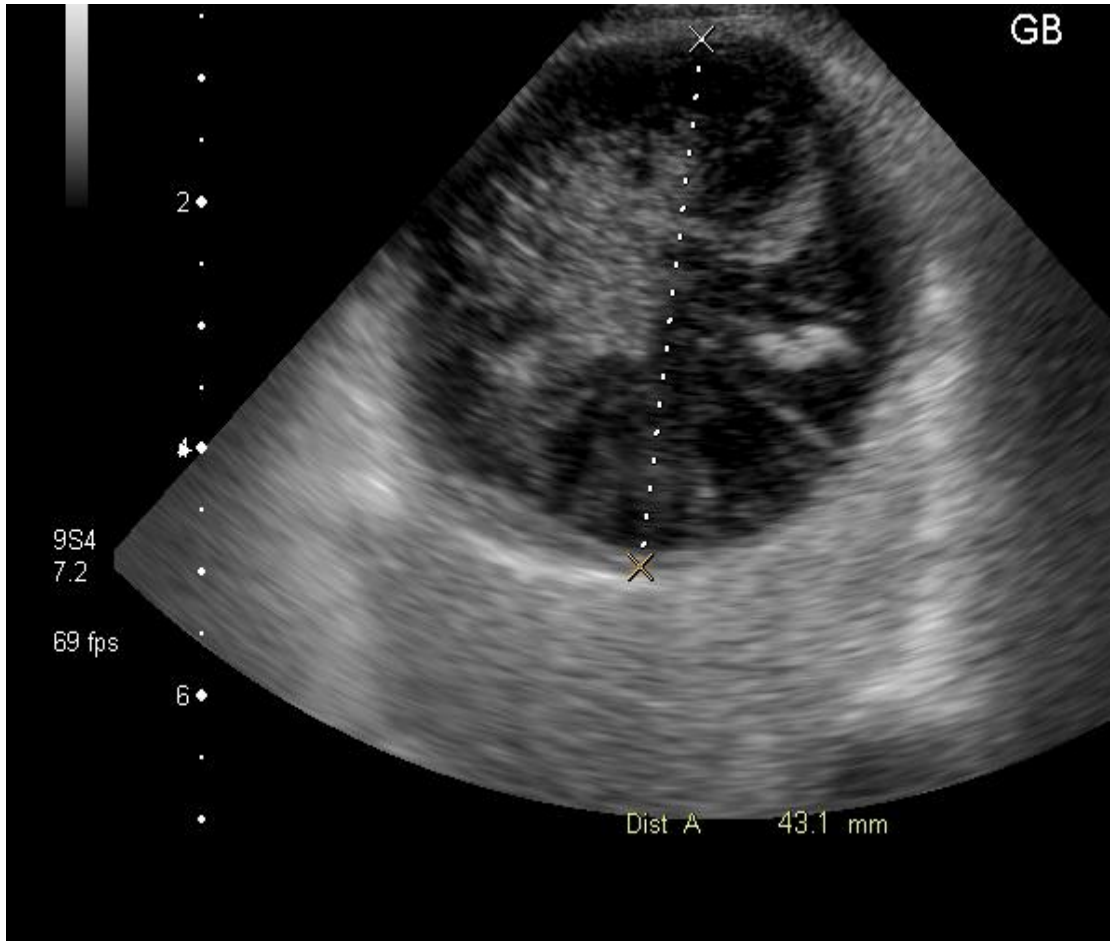
Abdominal ultrasound next. Supportive? Differentiate? Mucocele?

- Adrenomegaly
  - >0.7-0.75 cm, >0.6 cm small dogs
  - Unilateral
  - Bilateral
  - Incidentaloma?
- Hepatomegaly
- Gallbladder mucocele 30X more likely in dogs with Cushing's



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Do I have to differentiate PDH from ADH?

It’s a good idea.

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Why differentiate and how?

- Why?
  - Treatment and prognosis differ
  - Possible cure → adrenalectomy, hypophysectomy, radiation

- How?
  - LDDST
  - Abdominal ultrasound

- HDDST not much help
  - IF suppression at 8 hr = PDH
  - Lack of suppression either PDH or ADH

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LDDST *may* differentiate.

PDH if:

4 hr < 1.4 µg/dL OR

4 hr < ½ baseline OR

8 hr < ½ baseline (but above cut-off)

IF these are met = PDH

If not = PDH or adrenal tumor

35% with PDH don’t meet criteria

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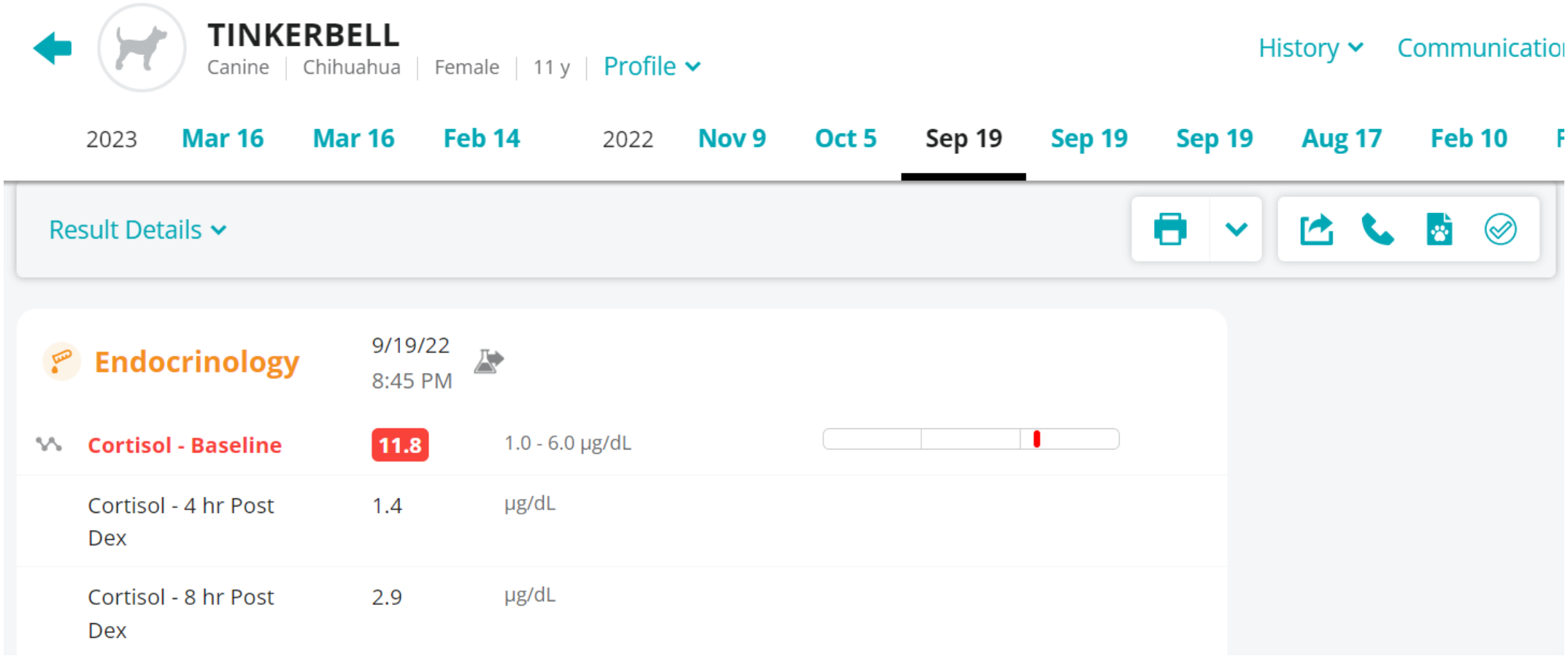

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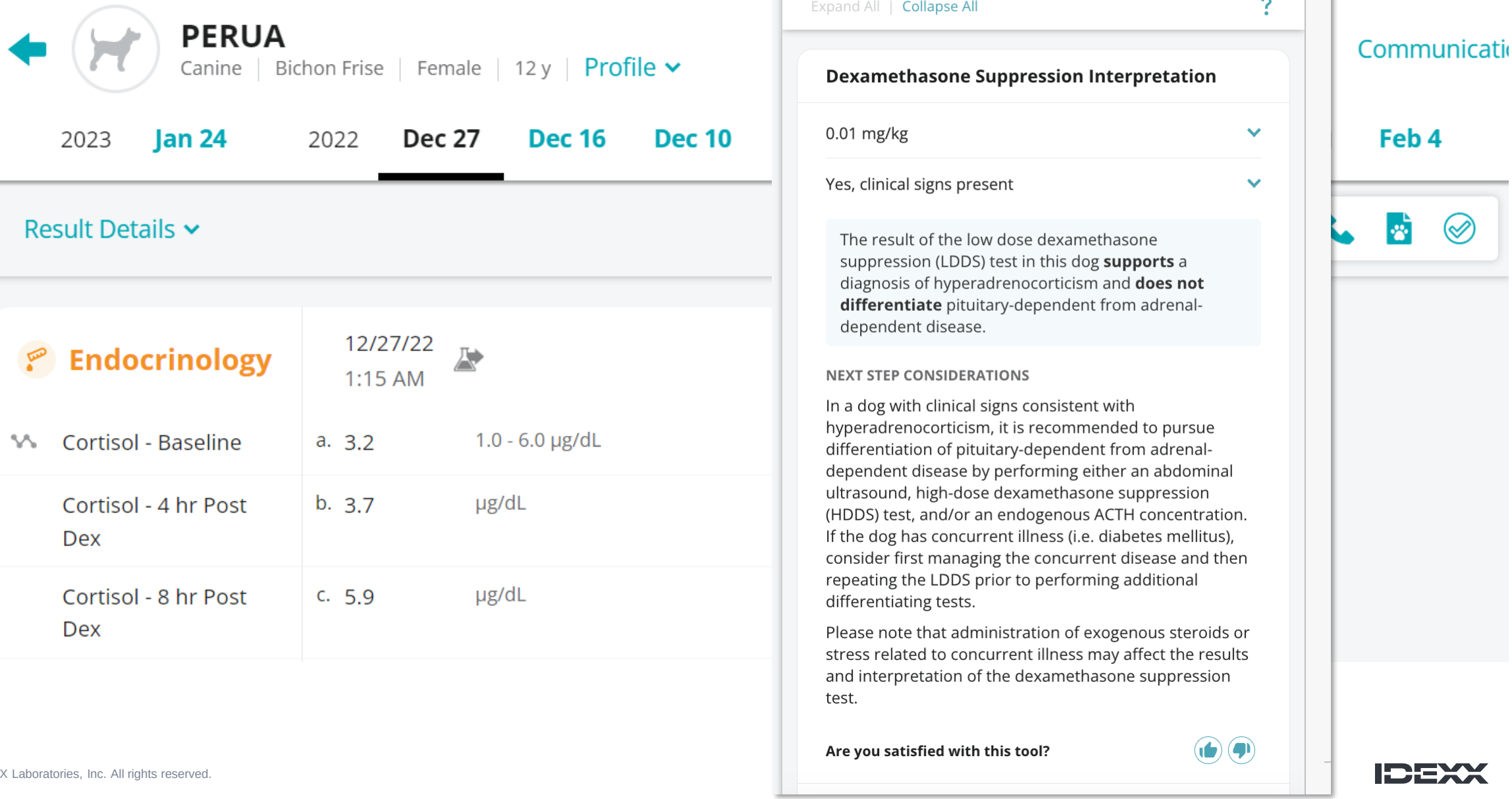

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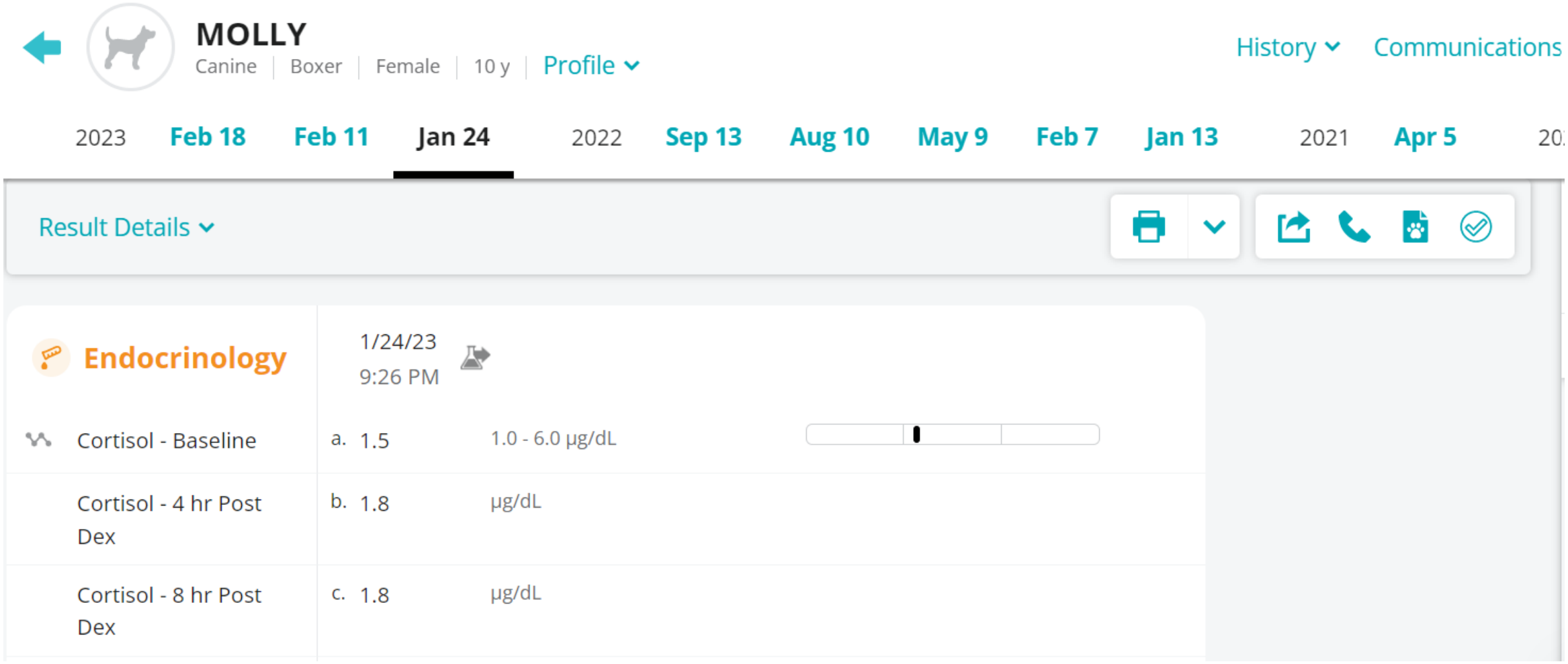

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My dog looks/acts cushingoid but LDDST is normal…

Take a deep breath and look at the patient.

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Suspect Cushing's but LDDST negative

- Any screening test can be negative when Cushing's present
  - Wrong (i.e., high) dose of dexamethasone
  - Disease too early or mild
- Review hx, PE, labs for other disease causing signs
- Mild signs, no complications → repeat LDDST in 3-6 months
- Strongly suspect, complications → ACTH stim test now

Complications: systemic hypertension, proteinuria, recurrent infection, dm…

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Does ‘atypical Cushing’s’ exist?

This is confusing…

Now called subdiagnostic Cushing’s syndrome.

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Subdiagnostic may just be mild/early Cushing's

- Cortisol cut-offs established decades ago
- Cut-offs may be too high
- Vary from lab to lab (as do cortisol assays)
- Normal animals have VERY LOW 4- and 8-hr cortisol values

8 hr cortisol (µg/dL)	Lab A cut-off 1.5 µg/dL	Lab B cut-off 1.0 µg/dL	Lab C cut-off 0.6 µg/dL
1.7	HAC	HAC	HAC
1.3	Normal	HAC	HAC
0.8	Normal	Normal	HAC
0.5	Normal	Normal	Normal

Normal dog should be <1

If not lower…

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Do I have to treat?

Please do. Your patient and client will thank you.

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Journal of Veterinary Internal Medicine

ACVIM
American College of Veterinary Internal Medicine

Open Access

Standard Article

J Vet Intern Med 2017;31:22–28

Comparison of Survival Times for Dogs with Pituitary-Dependent Hyperadrenocorticism in a Primary-Care Hospital: Treated with Trilostane versus Untreated

N. Nagata, K. Kojima, and M. Yuki

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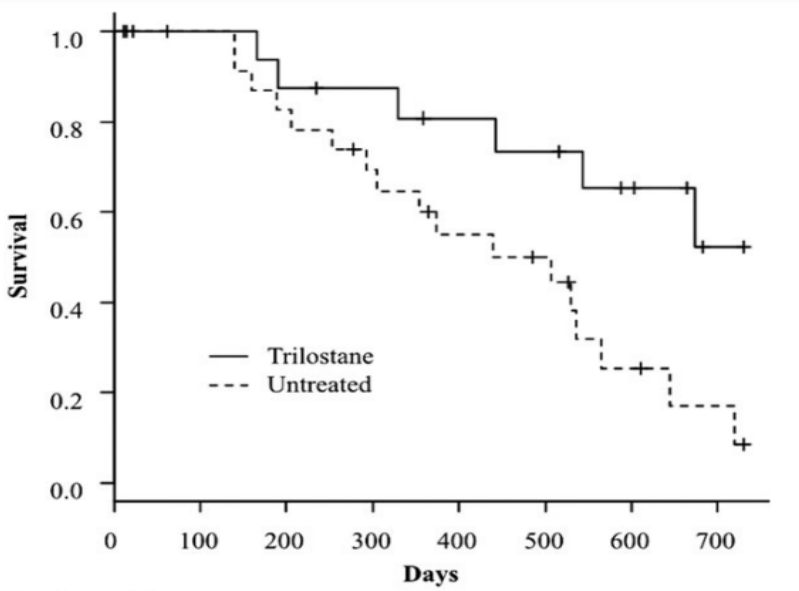
Withholding trilostane increased risk of death.

- Trilostane treatment 17 dogs
- No Trilostane 26 dogs
- Hazard ratio 5.01 in untreated
- 2-yr survival
  - Trilostane 52.2%
  - No treatment 8.5%
- Controlling cortisol excess important
  - ↓ risk of PTE, pancreatitis, systemic hypertension, infection, mucocele, dm…
  - **Better QOL**



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What is the starting dose of trilostane?

Glad you asked.

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Cushing's syndrome treatment

- Trilostane 0.5–1.5 mg/kg q12h
  - Survival longer with q12h dosing
  - BW > 25 kg may need lower dose
- **Name brand product only**
  - 5, 10, 20, 30, 60, 120 mg
  - Potency of compounded formulations variable
- Not free of side effects
  - Hypoadrenocorticism, usually transient
  - Adrenal necrosis, idiosyncratic, not dose-dependent, permanent or transient
  - Hyperkalemia and/or hyponatremia despite adequate control of cortisol

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Do I have to monitor with ACTH stim test?

Usually not.

Pre-pill cortisol in most instances.

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Pre-pill cortisol to monitor trilostane treatment

<1.4-2	1.4-2 to 5	>5
↓ dose 10% or ACTH stim	Continue current dose	Review history, PE USG SID v BID +/- Small dose ↑

ACTH stim test: 5 ug/kg IV Cortrosyn; 0, 1 hr post sample

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Cushing's Clinical Score

These are the important clinical signs to monitor in a dog with Cushing's. Please complete this and bring to your next monitoring consultation with your vet to help your vet monitor your dog's disease.

Please choose the number that best describes how your dog is today for each category.

Drinking & Urination

0	1	2	3
Drinks and urinates a normal amount	Possibly drinks and urinates more	Drinks and urinates more	Constantly drinking and urinating

Your dog's score

Appetite

0	1	2	3
Eats a normal amount	Finishes food more eagerly	Finishes food more eagerly & begs for more	More obsessed with food than ever

Your dog's score

Appearance

0	1	2	3
Appearance is normal	Slightly poor hair and skin quality	Poor hair and skin quality +/- slight pot belly	Substantial hair loss +/- pot belly

Your dog's score

Attitude/activity

0	1	2	3
Attitude/activity is normal	Not quite themselves	Not themselves +/- panting at rest	Not themselves, weak +/- constantly panting

Your dog's score

Any other clinical signs observed (e.g. vomiting, diarrhoea, off food):

To find out more visit www.canine-cushings.co.uk/monitoring

For further information contact: Dechra Veterinary Products Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire, SY4 4AS T +44 (0)1939 211200 F +44 (0)1939 211201 www.dechra.co.uk www.dechra.ie
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June 2020 DVP1411

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Do I need to worry about this in cats?

If a cat has fragile skin you do.

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Suspect Cushing’s syndrome in a cat if:

- DERM changes: skin hyper fragility syndrome (≈30%)
- Pendulous abdomen
- Folded ear tips (weak cartilage) rare but specific
- If PU/PD caused by diabetes, not Cushing’s
- No panting
- Increased BG, cholesterol, ALP (lipidosis, not steroid-induced)
  - ALP increase NOT as common in cats as dogs
- Skin changes more common than over diabetes mellitus

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Cushing’s syndrome in cats: diagnosis/treatment

- LDDST using **0.1 mg/kg IV**, 0, 4, 8 hr sample like dogs.
- Abdominal ultrasound to differentiate
- Cure if possible – adrenalectomy, hypophysectomy, radiation
- Trilostane
  - 5 mg BID, with food
  - (1-2 mg/kg q8-12h)

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Key takeaways:

- Cushing’s is a clinical syndrome caused by chronic cortisol excess
- Only screen pets that have multiple clinical and laboratory signs of disease.
- Differentiating pituitary for adrenal disease is optimal
- Use only name brand trilostane
- Rapid, accurate, in-house cortisol (Catalyst) makes diagnosis and monitoring easier

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Thank you!

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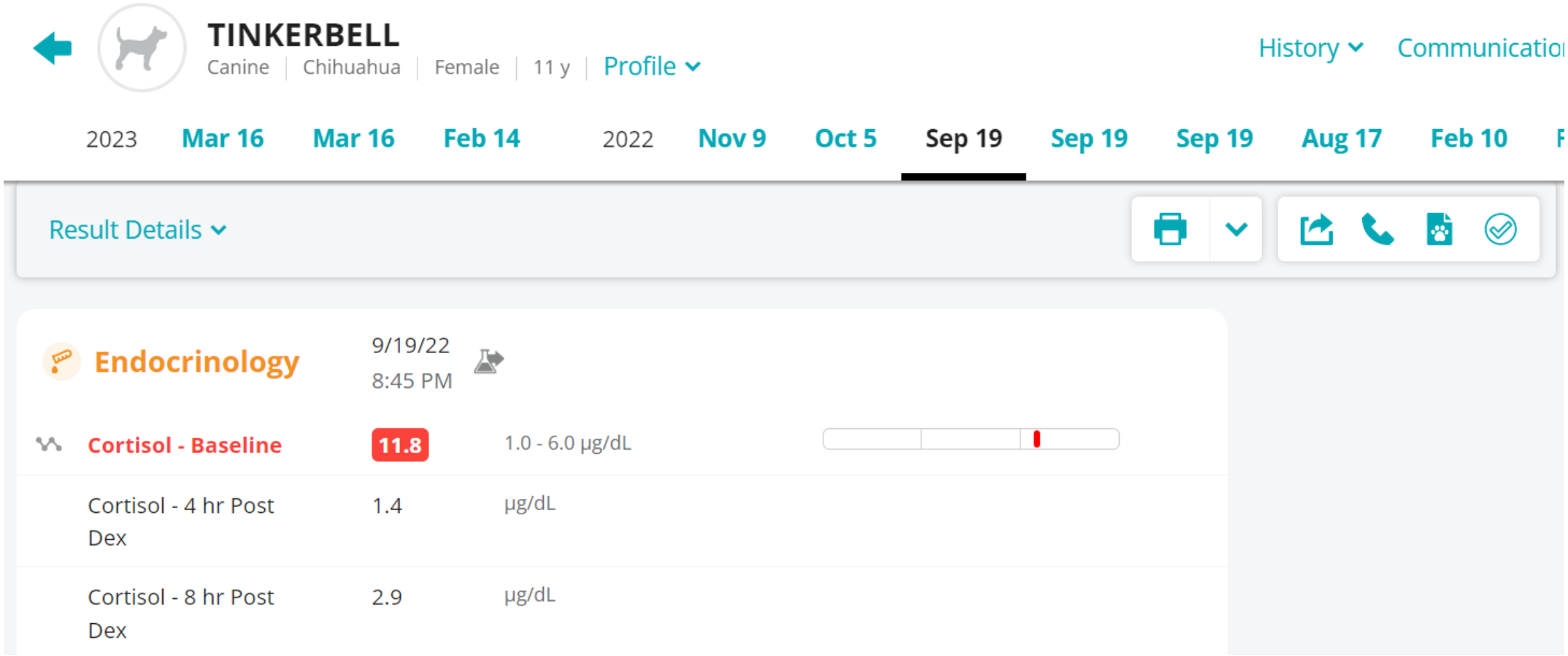
Does this dog have Cushing's syndrome?



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LDDST interpretation
(0.01 mg/kg dexamethasone IV then 0, 4, 8 hr cortisol)

1. Look at 8 hr result
2. If above cut-off consistent with Cushing’s syndrome

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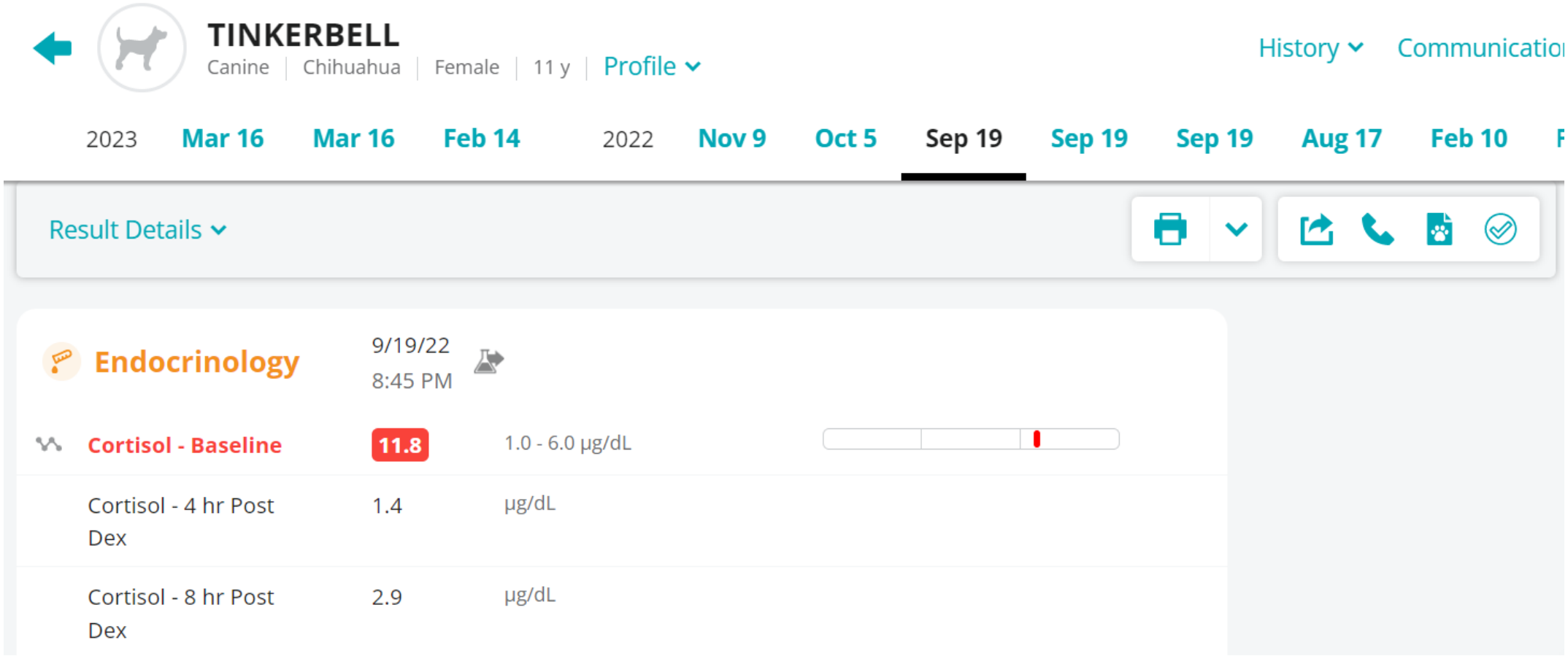
Does this dog have Cushing's syndrome?



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Should you differentiate between pituitary and adrenal disease?

Yes please…

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Why differentiate and how?

- Why?
  - Treatment and prognosis differ
  - Cure possible → adrenalectomy, hypophysectomy, radiation

- How?
  - LDDST
  - Abdominal ultrasound – adrenomegaly (unilat/bilat?), hepatomegaly
    - Both forms may be present in same dog
    - Gallbladder mucocele 30X more likely if Cushing's

- HDDST not much help
  - IF suppression at 8 hr = PDH
  - Lack of suppression either PDH or ADH

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LDDST interpretation to differentiate
(0.01 mg/kg dexamethasone IV then 0, 4, 8 hr cortisol)

1. Look at 8 hr result
2. If above cut-off consistent with Cushing's syndrome

3. THEN look at 4 (and 8) hr result to see if can discriminate. **PDH if**:
    - 4 hr cortisol below cut-off or
    - 4 hr cortisol <50% baseline or
    - 8 hr cortisol <50% baseline (and above cut-off)

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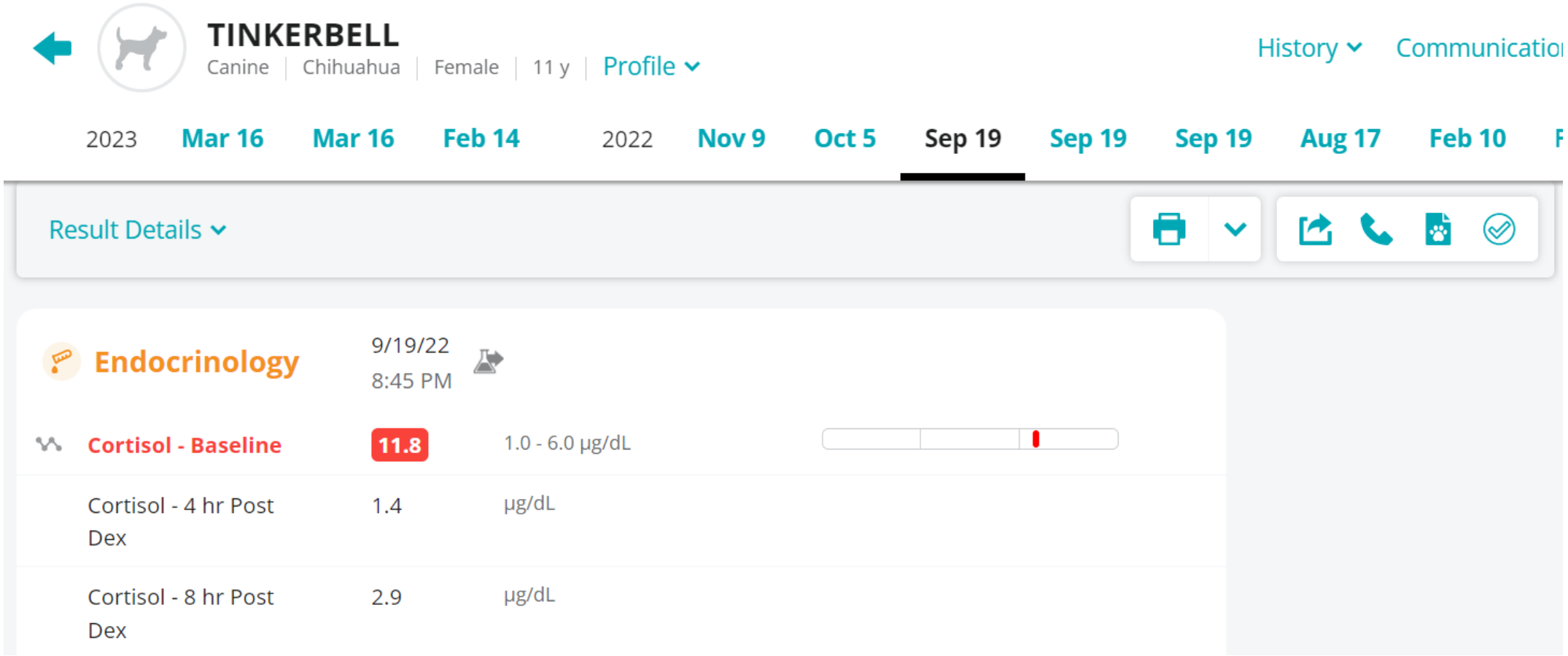

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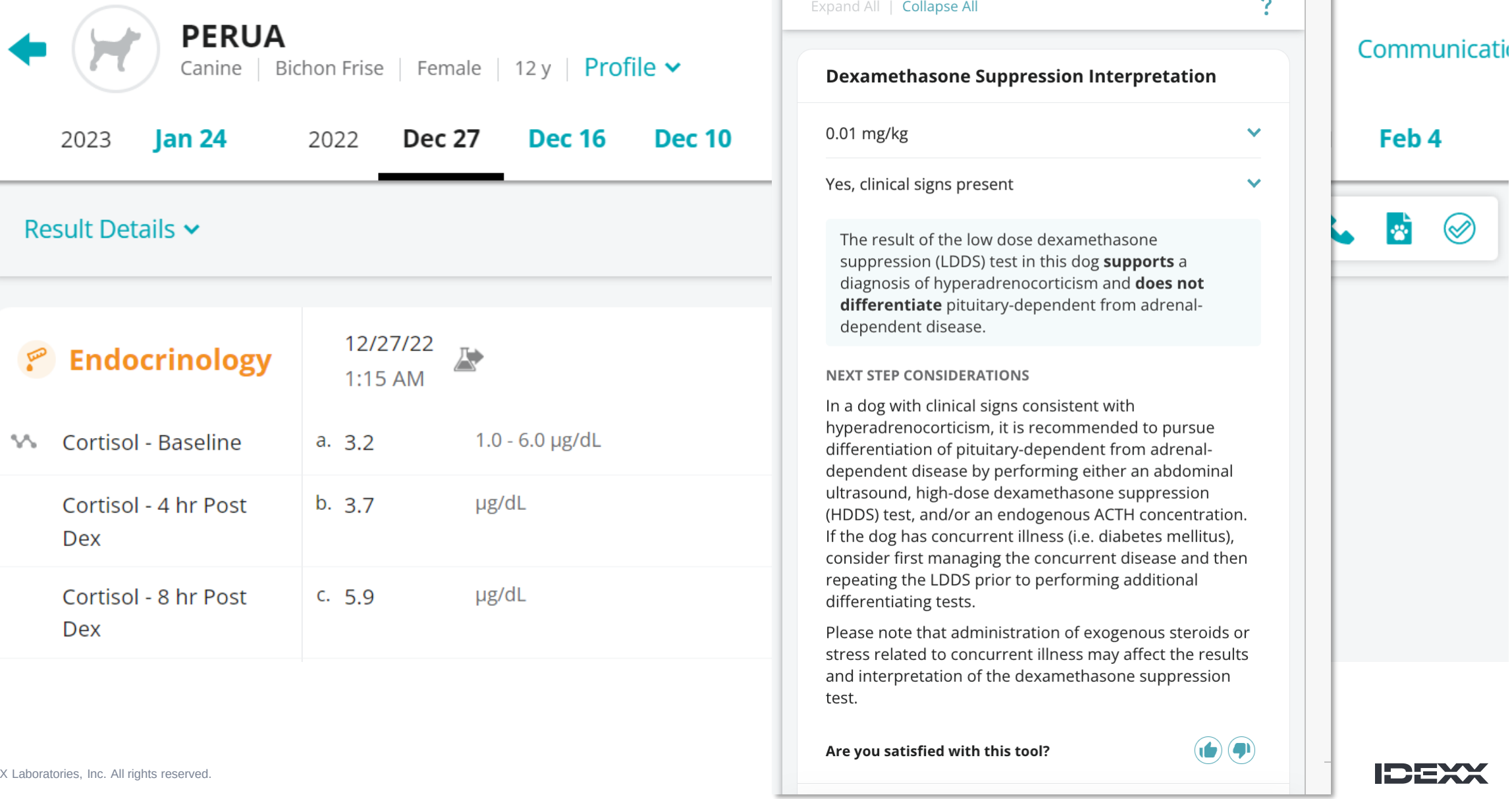

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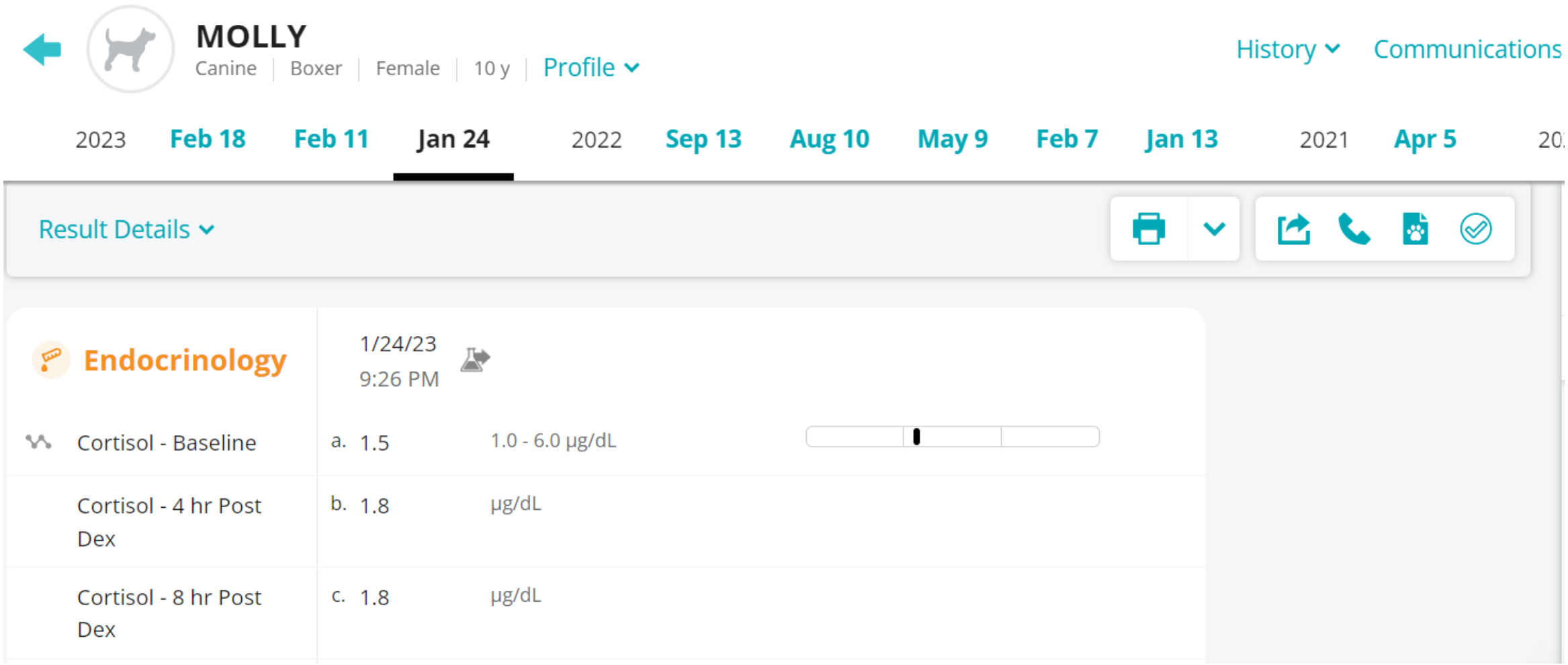

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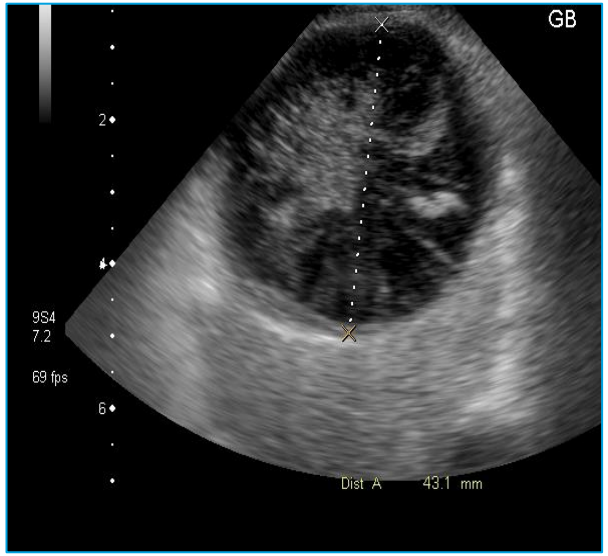
Abdominal ultrasound next

- Adrenomegaly
  - >0.7-0.75 cm, >0.6 cm small dogs
  - Unilateral
  - Bilateral
  - Incidentaloma? (size matters)
- Hepatomegaly
- Gallbladder mucocele 30X more likely in dogs with Cushing's



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My patient looks/acts cushingoid but LDDST is normal. Now what?

This is hard…

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Suspect Cushing's but LDDST negative

- Any screening test can be negative when Cushing's present
  - Wrong (i.e., high) dose of dexamethasone?
  - Mild disease too early to detect?
- Evaluate for other disease(s) as cause of signs.
- If mild signs (no complications) → repeat LDDST in 3-6 months
- If strongly suspect (or complications*) → retest now with ACTH stim test

* systemic hypertension, proteinuria, recurrent infection…

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Does subdiagnostic (formerly ‘atypical’) Cushing’s exist?

Now you’ve opened a can of worms…

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Subdiagnostic may just be mild/early ‘typical’

- Cortisol cut-offs established decades ago
- May be too high
- Vary from lab to lab (as do cortisol assays)
- Normal animals have VERY LOW 4- and 8-hr cortisol values

8 hr cortisol (µg/dL)	Lab A cut-off 1.5 µg/dL	Lab B cut-off 1.0 µg/dL	Lab C cut-off 0.6 µg/dL
1.7	HAC	HAC	HAC
1.3	Normal	HAC	HAC
0.8	Normal	Normal	HAC
0.5	Normal	Normal	Normal

Normal dog should be <1

If not lower…

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Journal of Veterinary Internal Medicine

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Standard Article

J Vet Intern Med 2017;31:22–28

Comparison of Survival Times for Dogs with Pituitary-Dependent Hyperadrenocorticism in a Primary-Care Hospital: Treated with Trilostane versus Untreated

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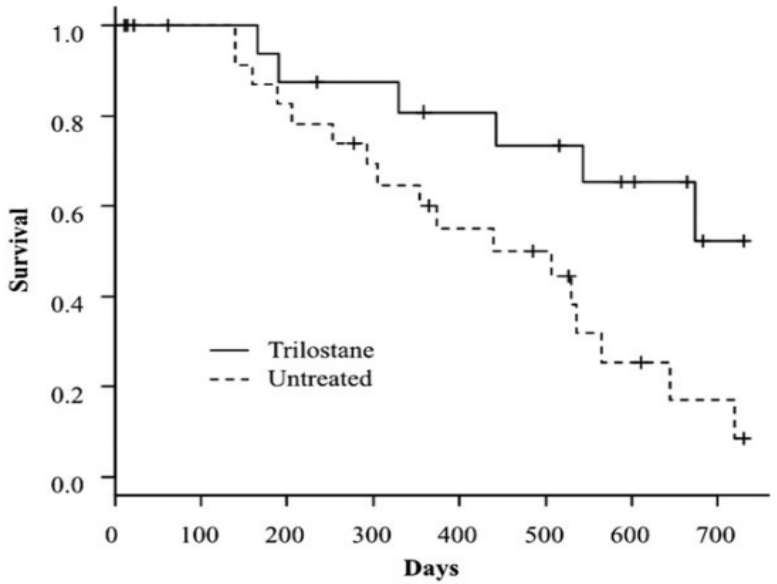
Withholding trilostane increased risk of death

- Trilostane treatment 17 dogs
- No trilostane 26 dogs
- **2 yr survival**
  - **Trilostane 52.2%**
  - **No treatment 8.5%**
- Controlling cortisol excess important
  - Less risk of pulmonary thromboembolism, diabetes mellitus, acute pancreatitis, systemic hypertension, infection, gallbladder mucocele
  - **Better QOL**



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Cushing's syndrome treatment

- Trilostane 0.5-1.5 mg/kg q12h
  - Survival longer with q12h dosing
  - BW >25 kg may need lower dose
- Name brand product only
  - Potency of compounded formulations variable
- Not free of side effects
  - Hypoadrenocorticism - usually transient
  - Adrenal necrosis - idiosyncratic, not dose-dependent, permanent or transient
  - Hyperkalemia and/or hyponatremia despite adequate control of cortisol
    - Recheck lytes during monitoring

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Do I need to do ACTH stims to monitor treatment?

Usually not.

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Clinically well-controlled dogs

- Pre-pill cortisol <1.4-2 µg/dL
  - ↓ dose by 10-20% or ACTH stim
- Pre-pill cortisol >1.4-2 µg/dL
  - Continue current dose
- Pre-pill cortisol >7 µg/dL
  - Re-evaluate history, USG, SID vs BID
  - CONSIDER small dose increase, based on CS/USG
    - Owner considerations

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Clinically Uncontrolled Dogs

- Pre-pill cortisol >5 µg/dL
  - Increase dose or split to BID
- Pre-pill cortisol 1.4-5 µg/dL (grey zone)
  - Split dose if SID
  - Maybe increase dose if >3 µg/dL?
  - Consider concurrent dz (DM?), stim if <3 µg/dL ?
- Pre-pill cortisol <1.4-2 µg/dL
  - Re-evaluate history, perform ACTH stim, +/- other diagnostics, consult with an internist

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Cushing's Clinical Score

These are the important clinical signs to monitor in a dog with Cushing's. Please complete this and bring to your next monitoring consultation with your vet to help your vet monitor your dog's disease.

Please choose the number that best describes how your dog is today for each category.

Drinking & Urination

0	1	2	3
Drinks and urinates a normal amount	Possibly drinks and urinates more	Drinks and urinates more	Constantly drinking and urinating

Your dog's score

Appetite

0	1	2	3
Eats a normal amount	Finishes food more eagerly	Finishes food more eagerly & begs for more	More obsessed with food than ever

Your dog's score

Appearance

0	1	2	3
Appearance is normal	Slightly poor hair and skin quality	Poor hair and skin quality +/- slight pot belly	Substantial hair loss +/- pot belly

Your dog's score

Attitude/activity

0	1	2	3
Attitude/activity is normal	Not quite themselves	Not themselves +/- panting at rest	Not themselves, weak +/- constantly panting

Your dog's score

Any other clinical signs observed (e.g. vomiting, diarrhoea, off food):

To find out more visit www.canine-cushings.co.uk/monitoring

For further information contact: Dechra Veterinary Products Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire, SY4 4AS T +44 (0)1939 211200 F +44 (0)1939 211201 www.dechra.co.uk www.dechra.ie
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Do I need to worry about this in cats?

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- Folded ear tips (weak cartilage) rare but specific
- PU/PD (caused by diabetes, not Cushing's)
- No panting
- Increased BG, cholesterol, ALP (lipidosis, not steroid-induced)
  - ALP increase NOT as common in cats as dogs
- Skin changes more common than over diabetes mellitus

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Cushing’s syndrome in cats: diagnosis/treatment

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- Cure if possible – adrenalectomy, hypophysectomy, radiation
- Trilostane
  - 5 mg BID, with food
  - (1-2 mg/kg q8-12h)

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Addison’s disease…or whatever we call it now.

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Then	Now
Addison’s disease	Hypoadrenocorticism
Atypical Addison’s disease	Eunatremic, eukalemic hypoadrenocorticism (EEH)
Addisonian crisis	Adrenal crisis
Relative adrenal insufficiency	Critical illness-associated corticosteroid insufficiency CIRCI

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Can I diagnose hypoadrenocorticism with resting cortisol?

Nope. ACTH stim test *required* for diagnosis.

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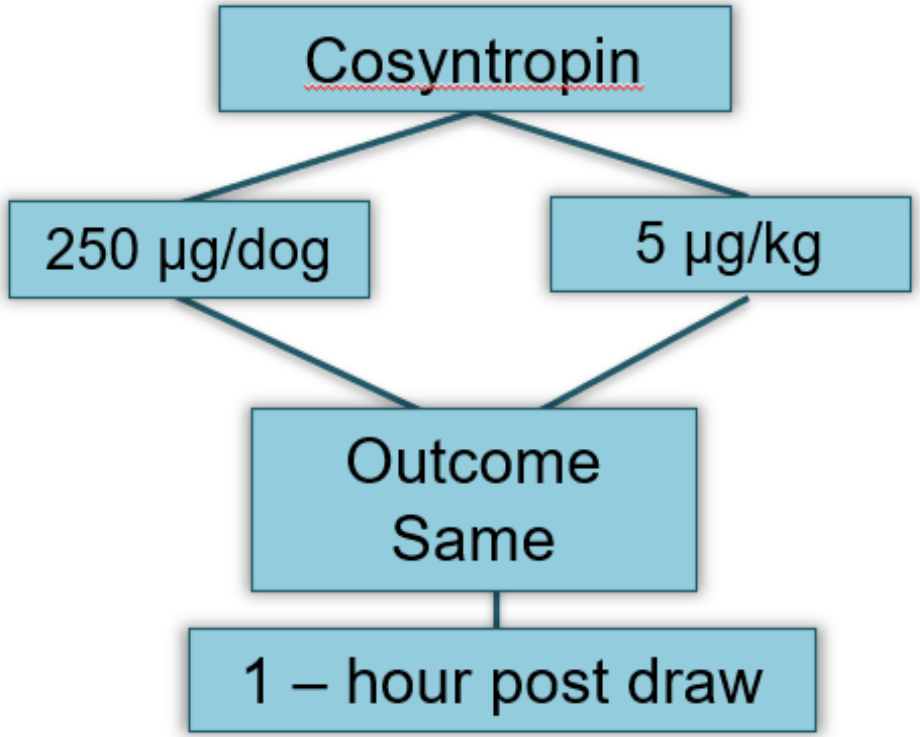
ACTH stimulation test



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DOI: 10.1111/jvim.15256

Journal of Veterinary Internal Medicine Open Access ACVIM American College of Veterinary Internal Medicine

STANDARD ARTICLE

Low-dose ACTH stimulation testing in dogs suspected of hypoadrenocorticism

Annabel Botsford[1,4] | Ellen N. Behrend[1] | Robert J. Kemppainen[2] | Philippe R. Gaillard[3] | Frank Oprandy[3] | Hollie P. Lee[1]

- Low dose: **1 µg/kg cosyntropin, IV**
  - NOT FOR CUSHING'S DIAGNOSIS!!!
- Reconstitute with 1 mL sterile saline
  - 250 µg/mL
- To make 10 µg/mL
  - Add 1 mL of 250 µg/mL to 24 mL saline
- To make 50 µg/mL
  - Add 1 mL of 250 µg/mL to 4 mL saline
- Store at -20° C (-4° F) for up to 6 months

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IDEXX

Is every sick dog an ‘atypical’ addisonian?
(Or in today’s terms: Does every sick dog have EEH?)

Right?

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EEH is indistinguishable from chronic GI disease

- 2 studies of dogs with chronic GI disease, resting cortisol <2 → ACTH stim
  - 4% final diagnosis hypoadrenocorticism (Hauck, et al. JVIM 2020)
  - 0.34% in a later study (Gallego, et al. JVIM 2022)

- Uncommon but life changing

- Repeat resting cortisol if first < 2 µg/mL?
  - Repeat was normal in 67% with first < 2 µg/mL (Gallego, et al. JVIM 2022)

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Suspect EEH when:
(30-40% with hypoadrenocorticism)

- Gastrointestinal signs
  - Megaesophagus…
- Albumin:globulin <1.08
  - Over 1/3 hyperglobulinemic
  - Hypoalbuminemia more common w EEH
- Low cholesterol (<133 mg/dL)
- Lack of stress leukogram in sick animal
  - Lymphocyte count >1500-1750cells/µL
  - Eosinophil count >500 cells/µL
- Reticulocytosis without anemia
- Increasing Ca, decreasing BG, regurgitation…

Formerly known as
Atypical Addison's

Reagan KL, McLarty E, Marks SL, et.. al. Characterization of clinicopathologic and abdominal ultrasound findings in dogs with glucocorticoid deficient hypoadrenocorticism. J Vet Intern Med. 2022;36(6):1947-1957. doi:10.1111/jvim.16564

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What fluid should I use to treat an adrenal crisis?

Good old LRs.

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Adrenal crisis: rethinking initial fluid choice

- LRs advantages
  - Contains buffer
  - Na^+ concentration lower than 0.9% NaCl
  - Trivial K (and Ca) concentration
- 0.9% NaCl concerns
  - Higher Na^+ concentration may raise serum Na too fast
    - Osmotic demyelination syndrome
  - Acidifying
  - Renal vasoconstriction due to high Cl^- concentration

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Emergency treatment

- IV fluids
  - 10-15 ml/kg bolus over 15-30 min, reassess, repeat prn
- IV dexamethasone
  - 0.1-0.2 mg/kg IV then 0.05 mg/kg q12h for 24-72 h
  - No prednis(ol)one or hydrocortisone until ACTH stim completed
  - No advantage to hydrocortisone CRI v dexamethasone injections
- Dextrose if hypoglycemic
  - 1 gm/kg 50% dextrose diluted 1:4 then add 2.5-5.0% to fluids
- Blood products if severe anemia (GI bleed)

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Maintenance treatment

- Prednisone
  - 0.1-0.2 mg/kg/day
    - OFTEN LOWER
  - 2-10X dose during stress or illness
- DOCP (deoxycorticosterone pivalate)
  - 1.1 mg/kg SQ/IM q28 days
  - DOCP has no glucocorticoid activity – never sole treatment
  - Consider even if electrolytes are normal (EEH)
- Monitor
  - Electrolytes at 14 days, then 28 days, eventually q3-6 months
  - CBC, biochemical panel, urinalysis at least yearly once stable
  - Lifelong

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Is hypoadrenocorticism a thing in cats?

Rare but in the news lately.

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STANDARD ARTICLE | Open Access

Clinical findings, treatment, and outcomes in cats with naturally occurring hypoadrenocorticism: 41 cases

Emma Roberts, Ian K. Ramsey, Ruth Gostelow, Anna Latysheva, Luca Battaglia, Paolo Silvestrini, Ghita Benchekroun, Karen Brenner, Bérénice Conversy, Riccardo Ferriani ... See all authors

First published: 11 December 2024 | https://doi.org/10.1111/jvim.17243

Hypoadrenocorticism in cats: a 40-year update

Magdalena J Glebocka and Alisdair Boag

Journal of Feline Medicine and Surgery
1–7
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Sage

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access
ACVIM American College of Veterinary Internal Medicine

Clinical features and long-term management of cats with primary hypoadrenocorticism using desoxycorticosterone pivalate and prednisolone

Nadja S. Sieber-Ruckstuhl[1] | Livia Harburger[1] | Natalie Hofer[1] | Claudia Kümmerle[1] | Claudia Müller[1] | Barbara Riond[2] | Regina Hofmann-Lehmann[2] | Claudia E. Reusch[1] | Felicitas S. Boretti[1]

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Hypoadrenocorticism cat style…

- Autoimmune, trauma, lymphoma, congenital (2 cats <12 mo)
- Clinical signs and lab findings like dogs (lack of stress leukogram)
- Hypercalcemia in 32% (iCa)
- EEH exists in cats (some zero aldosterone pre-, post stim)
- Low cobalamin, low TLI (EPI) in some
- ACTH stim 5 mcg/kg, 125 mcg/cat IV, IM, 30- and 60-min post samples
- Treatment similar to dog but caution re volume overload
- DOCP dose 2.2 mg/kg (higher than dog)

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Most common adrenal disease in cats?

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Primary hyperaldosteronism

- Most common feline adrenal disease
- Hypokalemia, hypertension
- Progressive renal / cardiac damage due to aldosterone AT1 receptor effects
- Unilateral adrenal carcinoma or adenoma most common
- Diagnosis → adrenal mass, ↑ basal aldosterone + hypokalemia usually sufficient
- Treatment
  - Surgery → Adrenalectomy
  - Medical → Spironolactone 2 mg/kg q12h, amlodipine 0.1–0.2 mg/kg q24 h, K gluconate 1–6 mEq/cat q12h

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Case “Munou”

IDEXX VetConnect PLUS | Home | Directory of Services | Imaging | Telemed

MUNOU [redacted]38174
Feline | Feline, Mixed Breed | Male | 11 y | Profile

	2023 Feb 28	2022 Dec 15	Feb 12	Jan 12	2021 Dec 2
Sodium	156	155	154		
Potassium	3.3	3.7	3.5		
Na: K Ratio	47	42	44		
Chloride	115	114	111		
TCO2 (Bicarbonate)	26	28	26		

Chloride	115	114 - 126 mmol/L	114	111	
TCO2 (Bicarbonate)	26	12 - 22 mmol/L	28	26	
Anion Gap	18	12 - 25 mmol/L	17	21	
Total Protein	7.0	6.3 - 8.8 g/dL	7.5	7.3	
ALT	33	27 - 158 U/L	37	37	
ALP	21	12 - 59 U/L	14	17	
Hemolysis Index	b. N		e. N	h. 1+	
Lipemia Index	c. N		f. N	i. N	

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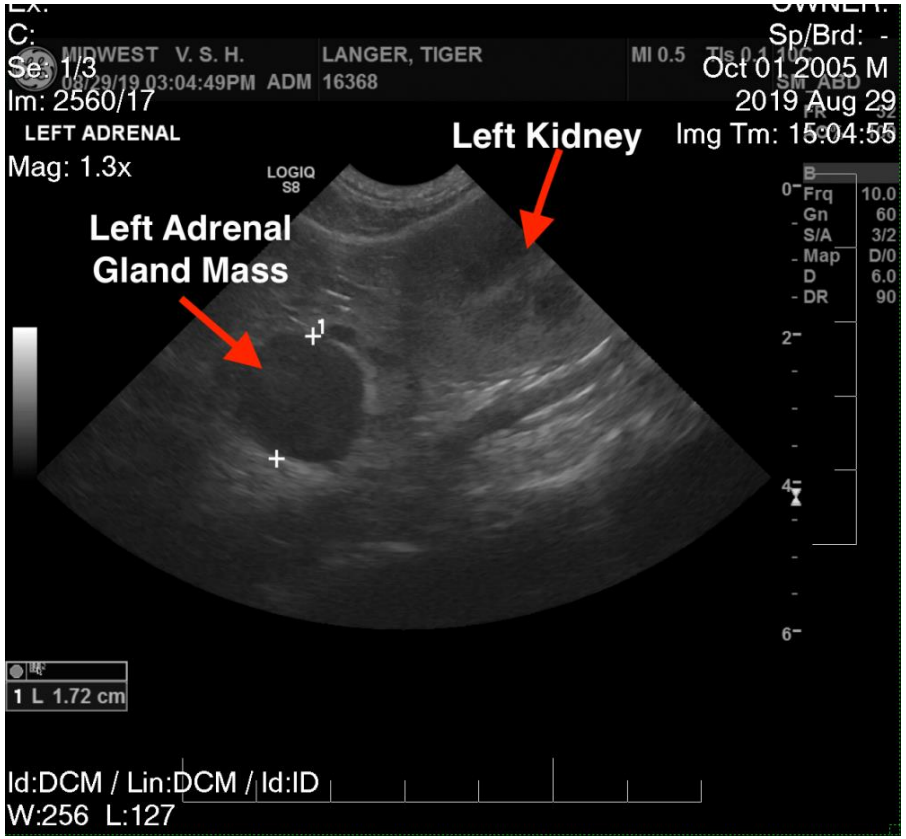
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Left Kidney
Left Adrenal Gland Mass
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Frq 10.0
Gn 60
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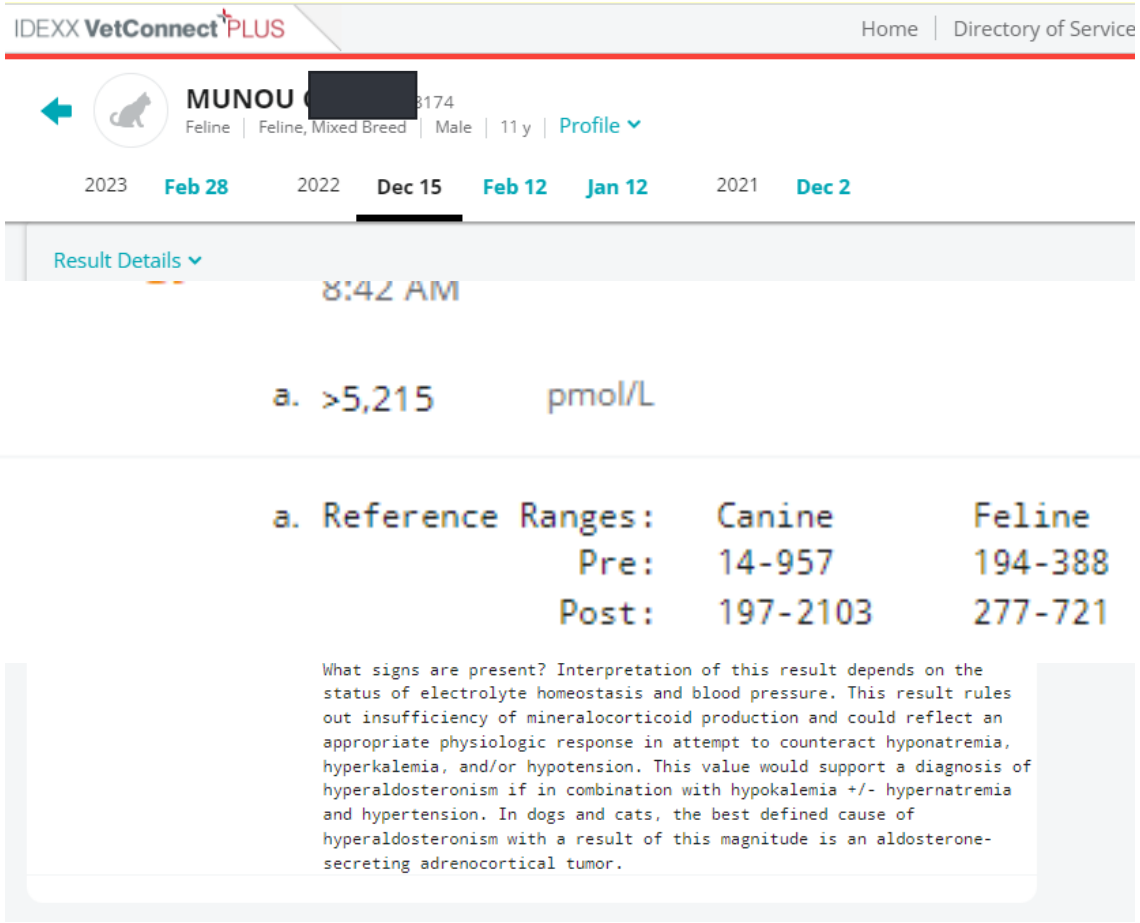

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Thank you.

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