CREATING CLARITY

The collapsed DKA, cushingoid patient: and other confusing endocrine comorbidities.

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Bill Saxon, DVM, DACVIM, DACVECC

IDEXX

Disclosure:

Bill Saxon is a full-time employee of IDEXX.

You’re on clinics and in walks…

A collapsed shocky dog with abdominal pain….

Everyone’s favorite combo:

- Acute pancreatitis
- Diabetic ketoacidosis
- Pot-bellied Dachshund…Cushing’s too?

Where to begin…

Forget about Cushing's for now.
Unless on trilostane.

- Avoid testing sick pets for Cushing's
- LDDST weeks-months after acute dz controlled
- ACTH stim if must test when sick
  - Higher specificity 90% v 70% LDDST = fewer false +

- If on trilostane → r/o adrenal crisis
  - Cortisol or ACTH stim

Tackle the DKA

- Ketosis = diabetes mellitus *plus* something else
  - Counterregulatory hormones → ketone production
- IV fluids to restore volume, hydration, ongoing losses…
- Insulin required
  - Regular insulin intermittent IM injection
    - 0.2 U/kg once then 0.1 U/kg q1h
  - Regular insulin CRI

Add 1-2 U/kg to 240 ml saline
BG >400 = 20 ml/h, 0% dextrose
BG 250-400 = 10 ml/h, 0% dextrose
BG 150-250 = 5 ml/h, 2.5% dextrose
BG 80-150 = 0 ml/h, 5.0% dextrose
BG <80 = 0 ml/h, 5.0% dextrose, 1 m/kg 50% dextrose bolus

Confirm and treat pancreatitis

- Opioid analgesia now
- LRs likely best fluid
  - Lactate anti-inflammatory properties
- In clinic testing for pancreatitis
  - SNAP cPL → *screening* test, if positive Spec cPL
  - Catalyst pancreatic lipase → *diagnostic* test
- Panoquell®-CA1
  - 0.4 mg/kg IV SID x 3 d, over 15-60 sec
- Enteral nutrition w/in 48 hr of onset of signs
  - Maropitant 1 mg/kg q24h SC, IV over 1 min
- C-reactive protein anyone?
  - IF increased = systemic inflammation, monitor daily, persistent increase poor prognosis

Crisis over for a while, diabetes unregulated.

Does the dog have Cushing’s syndrome?

Diagnosing Cushing's in known diabetic

- Cushing's most common cause of insulin resistance in dogs
- Suspect concurrent Cushing's syndrome when:
  - Lack of response to or short/variable duration of insulin
  - Increased glucose variability, post-prandial hyperBG (CBGM)
  - PU/PD (USG <1.020) despite decent glucose regulation
  - Hypertriglyceridemia
  - Panting, derm changes, pot belly, hepatomegaly…

Cushing’s testing in known diabetic

- 2-4 wk or longer after start of DM treatment
- **When weight loss stops**
  - **Suggests adequate control of DM**
- LDDST if dog stable
- ACTH stim if still ‘off’
  - Consider positive with post-ACTH cortisol >?

Do you decrease insulin dose when starting trilostane?

Usually not necessary…

Treating newly-diagnosed Cushing's in a diabetic

- Trilostane, 1-1.5 mg/kg PO BID WITH FOOD
  - No insulin dose decrease needed, usually
- Monitor with ACTH stimulation testing or pre-pill cortisol
  - 2 weeks after starting trilostane
  - 1 month later
  - 3 months later
- Focus on control of HAC before fine-tuning insulin
  - CLINICAL SIGNS CONTROLLED
  - FreeStyle Libre may allow more rapid insulin dose adjustments

Flipping the script:

Dog has Cushing’s syndrome, cortisols ok.

Still pu/pd…

Is it also a diabetic?

SUNNY (via email…)

I was hoping you possibly had time to discuss a case. Sunny [redacted] is a 13 yr old neutered dachshund referred to LSU IM for elevated liver enzymes. After his visit with LSU, we performed LDDST and confirmed Cushings. Initially started Vetoryl at 1 mg/kg BID. Resting cortisol (pre-trilostane) 2 weeks later was 2.7. Clinical signs are not controlled (PU/PD, lethargic at home). I then increased Vetoryl to 2 mg/kg in the morning and 1 mg/kg in the evening. Clinical signs not improving and now owner is reporting urinary incontinence. Resting Cortisol yesterday is 5.0. Other considerations, he has a 4 lb weight loss over the last couple months, currently on Vetmedin and overall just looks terrible.

Am I ok to increase to 2mg/kg BID. Should I increase it? Should I culture the urine?

Dr. Lathan answered…

I suspect that you have room to increase with the resting cortisol of 5. But geez, that weight loss is definitely not typical of Cushing's.

Urine culture is reasonable, although checking a chem may be helpful. It's possible he decided to develop DM, as well (would pick that up on UA). Another thought is making sure he doesn't have a macroadenoma causing decreased appetite and lethargy. I assume his appetite hasn't picked up recently? Has it gotten worse?

Sunny’s vet said…

Good morning. Wanted to let you know Sunny's blood glucose was 612 yesterday with 1+ glucosuria, 1+ ketonuria. No evidence of UTI. ALP has decreased from 9000 to 2600. Also the PrecisionPSL is elevated at 205 (normal is 24-140).

Suspect DM in a known cushingoid when:

- Weight loss
- PU/PD persists despite cortisol suggesting HAC controlled
- Blood glucose trending up or mildly increased
- Fructosamine increased
- Check UA in dogs with Cushing’s when signs don’t fit

Diabetes mellitus causes weight loss.

Cushing’s syndrome does not.

Treating diabetes in known cushingoid.

- Caninsulin®, NPH BID
  - Higher end of starting range (0.25-0.5 U/kg q12h)
  - Basal insulin may help decrease glycemic variability
    - Degludec (0.5 U/kg SID to start) or glargine U-300
- Split trilostane to BID dosing if currently SID
  - Same DAILY dose
  - Example: 60 mg SID = 30 mg BID
- Monitor as usual
  - CLINICAL SIGNS, weight, glucose monitoring
  - Pre-pill cortisol or ACTH stim test for HAC
- Try not to micromanage DM—focus on clinical signs!
  - Otherwise exhausting to owners…

You have a diabetic cat showing insulin resistance...

What endocrine diseases come to mind?

Cats with unregulated diabetes mellitus…

- CGBM to assess insulin resistance, glucose variability, Somogyi…
- Rule out infection, hyperT4, pancreatitis…
- Cushing's syndrome?
  - No pu/pd unless diabetic
  - Skin hyper-fragility (folded over ear tips)
  - LDDST using 0.1 mg/kg dexamethasone
- Hypersomatotropism?
  - 25% diabetic cats
  - Lack of weight loss or weight gain (some lose wt)
  - IGF-1 after 4-8 wk of insulin
    - If test at diagnosis of dm pick up 2/3
    - If delay 8-10 wk pick up all
  - Hypophysectomy, stereotactic radiation, pasireotide, cabergoline
    - Increase insulin, some plateau above 10-15 U/injection

Chemistry

	1/18/23 4:12 AM	9/22/22 6:04 AM	1/16/21 8:49 PM	10/2/20 11:08 PM	9/22/20 11:35 PM	10/11/19 11:09 PM	9/29/18 2:46 AM
Glucose	d. **546**	**381**	128		127	138	104
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TCO2 (Bicarbonate)	17	22	20		16		
Anion Gap	24	21	19		17		
Total Protein	**9.1**	8.4	8.0		7.5		
Albumin	3.7	3.4	3.5		3.2		
Globulin	5.4	5.0	4.5		4.3		
Albumin: Globulin Ratio	0.7	0.7	0.8		0.7		
ALT	29	27	34		56		
AST	**10**	**10**	**14**		23		
ALP	55	45	26		26		
GGT	2	1	1		1		
Bilirubin - Total	0.2	0.3	0.2		0.2		

Endocrinology

1/18/23 4:14 AM

Insulin-like Growth Factor 1	a. **338**	12 - 92 nmol/L	

a. Referral test performed at Michigan State University.

Endocrinology Interpretation
The serum concentration of insulin-like growth factor 1 (IGF1) is increased and acromegaly is a likely differential diagnosis.
It is recognized that increases in this hormone may occur as a metabolic response to diabetes mellitus in some cats, but this result is clearly higher than what would be expected in that case.
Typical physical changes associated with acromegaly would further support such a diagnosis.
Cheryl C. Rice, DVM, DACVIM (SAIM)
Assistant Professor, Endocrinology

A diabetic cat presents sick. Glucose is normal.

First question: is it on an SGLT2 inhibitor?

Euglycemic DKA in cats on SGLT2 inhibitors. Tricky.

- Ketosis, acidosis, BG <250 mg/dl (sometimes much lower)
  - If blood gas not available ketosis with normal BG sufficient
- Highest risk within 1st 2 weeks of starting drug (86%)
- No hyperglycemia due to increased renal loss and depleted glycogen stores
- Some insulin (Type 2 DM) but not enough to prevent ketosis
- Ketosis = diabetes plus disease
  - CBC, biochemistry, UA, pancreatic lipase, retroviral screen to identify
- Use ketone meter for earlier detection of ketones (beta-hydroxybutyrate)
  - Urine dipstick (acetoacetate) fine if all you have

Clinically no different from 'standard' DKA – awareness is key to diagnosis.

Consider with euglycemia, mild hyperglycemia, or mild hypoglycemia…

Grab bag…

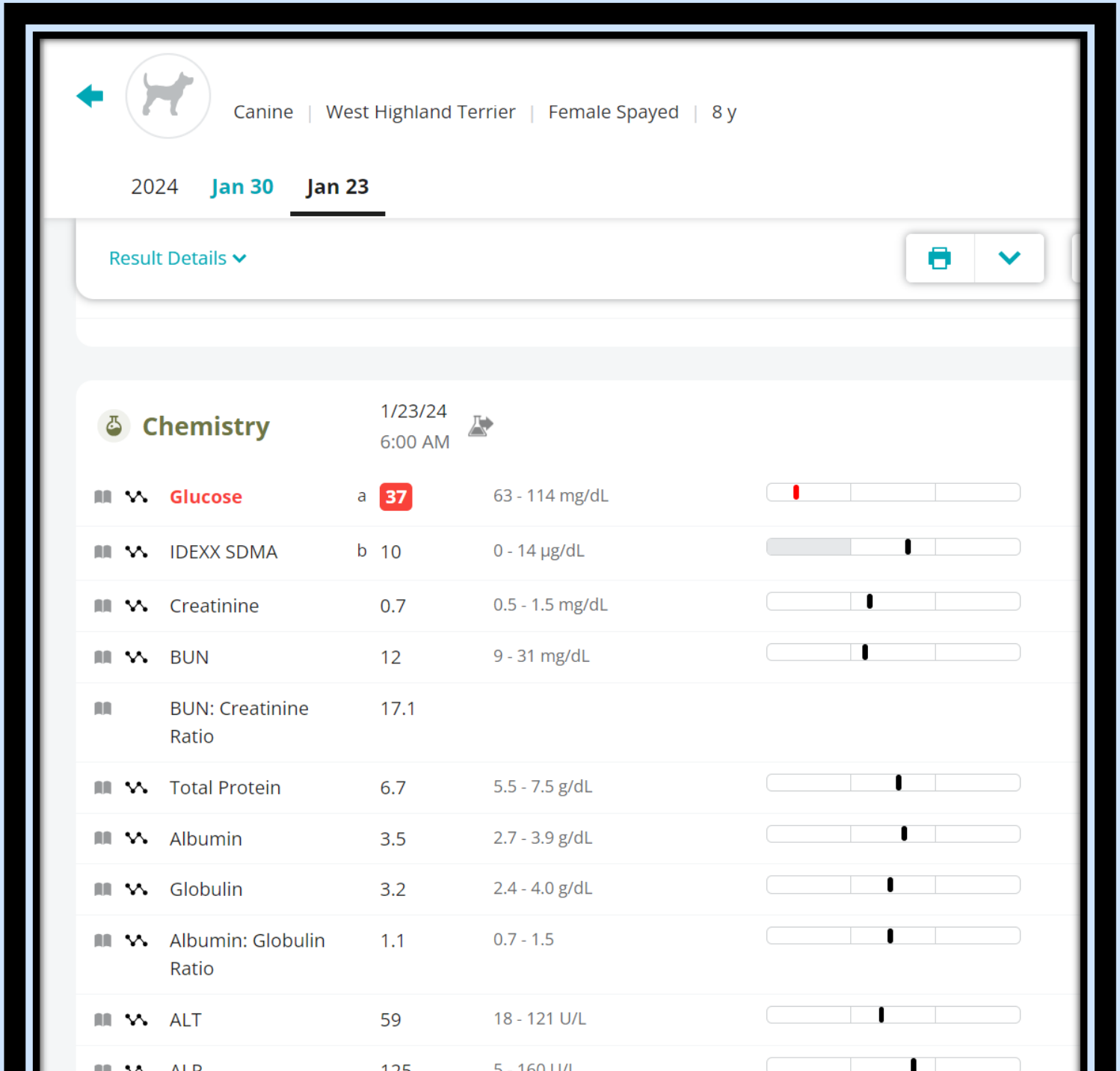
Severe hypoglycemia… Insulinoma?

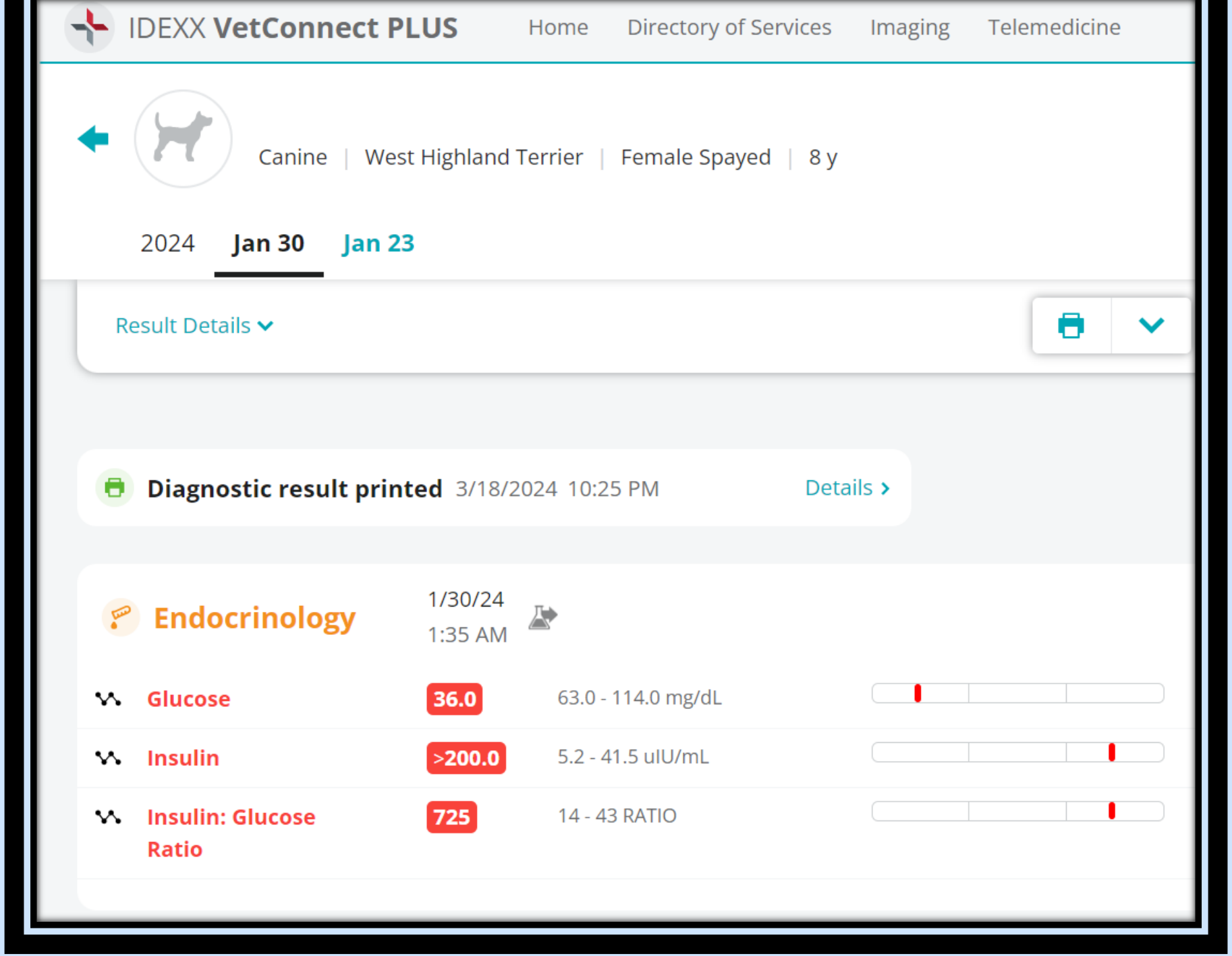
- Other causes ruled out?
- Blood glucose <60 mg/dL (ideally <50 mg/dL)?
- Submit insulin glucose panel
- If BG on panel >60 mg/dL cannot interpret
  - Insulin:glucose ratio not helpful
- If BG <60 mg/dL…

What should insulin be when blood glucose is low?

LOW.

Therefore, if insulin is increased (OR NORMAL) = insulinoma.


Canine | West Highland Terrier | Female Spayed | 8 y
2024
Jan 30
Jan 23
Result Details
Chemistry
1/23/24
6:00 AM
Glucose a 37 63 - 114 mg/dL
IDEXX SDMA b 10 0 - 14 µg/dL
Creatinine 0.7 0.5 - 1.5 mg/dL
BUN 12 9 - 31 mg/dL
BUN: Creatinine Ratio 17.1
Total Protein 6.7 5.5 - 7.5 g/dL
Albumin 3.5 2.7 - 3.9 g/dL
Globulin 3.2 2.4 - 4.0 g/dL
Albumin: Globulin Ratio 1.1 0.7 - 1.5
ALT 59 18 - 121 U/L


IDEXX VetConnect PLUS
Home
Directory of Services
Imaging
Telemedicine
Canine | West Highland Terrier | Female Spayed | 8 y
2024
Jan 30
Jan 23
Result Details
Diagnostic result printed 3/18/2024 10:25 PM
Details
Endocrinology
1/30/24
1:35 AM
Glucose
36.0
63.0 - 114.0 mg/dL
Insulin
>200.0
5.2 - 41.5 uIU/mL
Insulin: Glucose Ratio
725
14 - 43 RATIO

Hypercalcemia…Primary hyperparathyroidism?

- Other causes ruled out?
- IONIZED calcium increased?
- Submit iCa PTH panel (+/- PTHrp)
- If iCa normal cannot interpret
- If iCa increased…

What should PTH be when blood iCa is high?

LOW.

Therefore, if PTH is increased (OR NORMAL) = primary hyperparathyroidism.

TEST		RESULT	REFERENCE VALUE	
Ionized Calcium	a	**1.55**	**1.25 - 1.45 mmol/L**	H

a Referral test performed at Michigan State University.

Endocrinology

TEST		RESULT	REFERENCE VALUE	
Parathyroid Hormone	a	**12.20**	**1.10 - 10.60 pmol/L**	H
Parathyroid Related Protein	b	0.0	0.0 - 1.0 pmol/L	

TEST		RESULT	REFERENCE VALUE		
Ionized Calcium	[a]	**1.52**	**1.25 - 1.45 mmol/L**	H	**1.55**

[a] Referral test performed at Michigan State University.

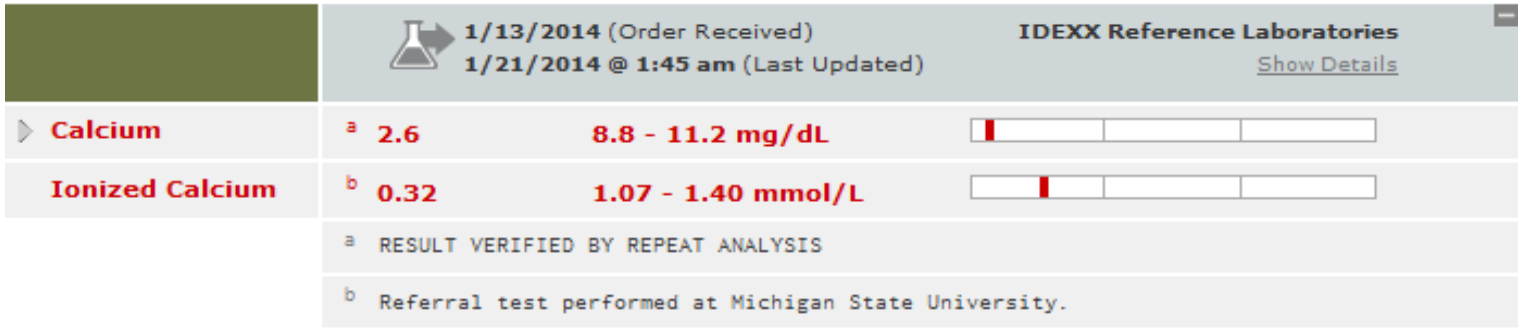
Endocrinology

TEST		RESULT	REFERENCE VALUE	
Parathyroid Hormone	[a]	5.70	1.10 - 10.60 pmol/L	3.00
Parathyroid Related Protein	[b]	0.0	0.0 - 1.0 pmol/L	

Hypocalcemia…Primary hypoparathyroidism?

	1/13/2014 (Order Received) 1/21/2014 @ 1:45 am (Last Updated)		IDEXX Reference Laboratories Show Details
Calcium	[a] 2.6	8.8 - 11.2 mg/dL	
Ionized Calcium	[b] 0.32	1.07 - 1.40 mmol/L	
	[a] RESULT VERIFIED BY REPEAT ANALYSIS		
	[b] Referral test performed at Michigan State University.		

Hypocalcemia…Primary hypoparathyroidism?



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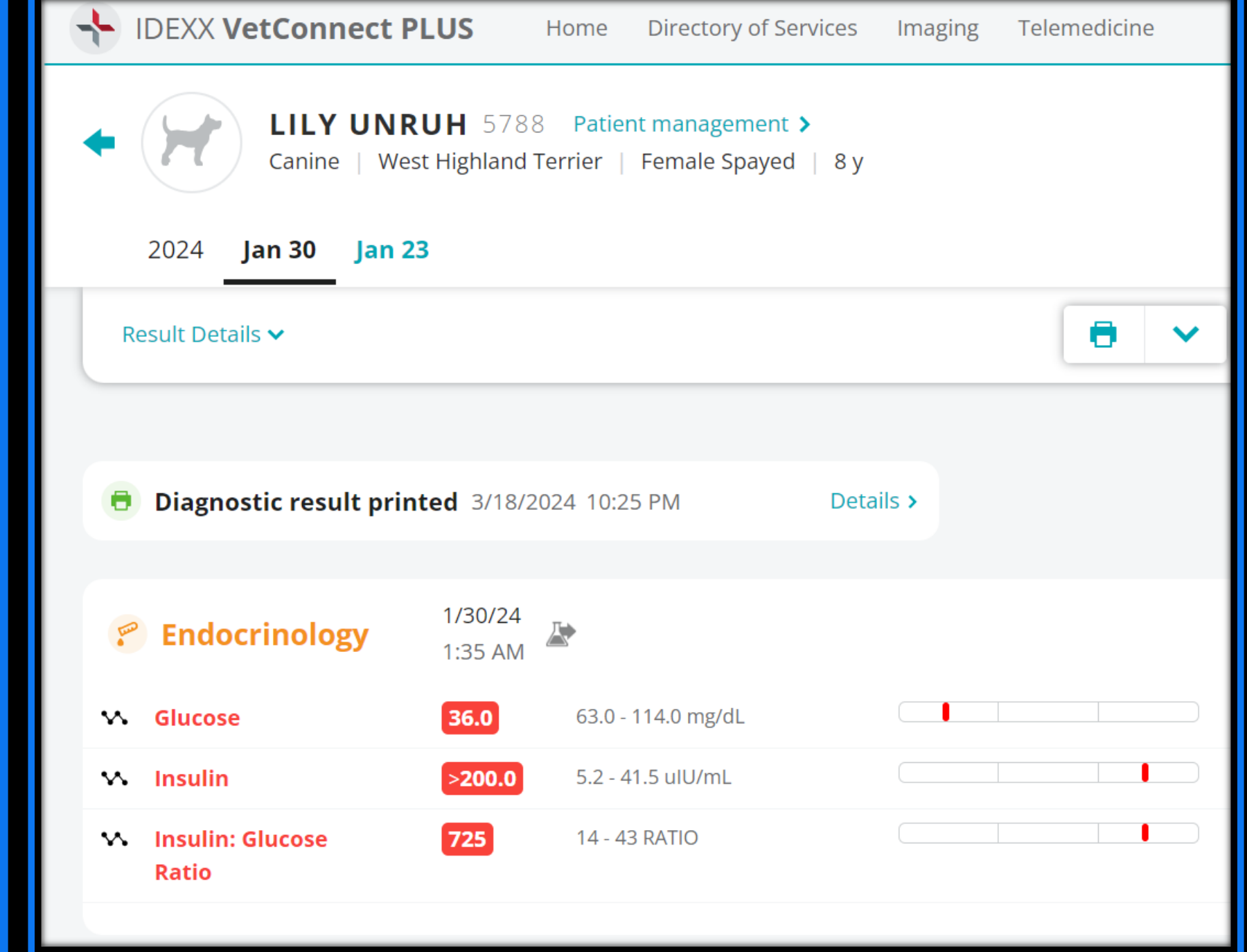
Thank you!

Grab bag…



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Thank you!

Test interpretation practice!

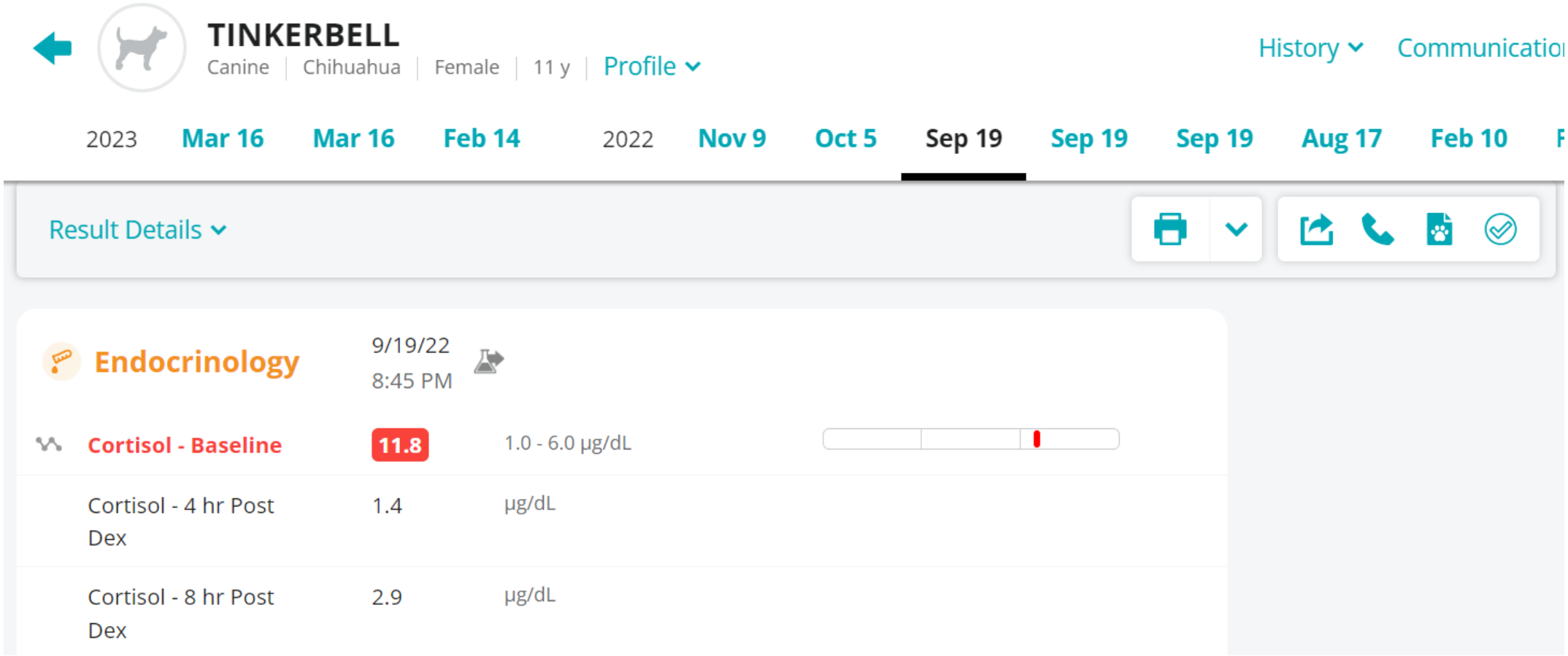
LDDST: *Screening* Interpretation

(***USE YOUR LAB'S NUMBERS!)

1. DO NOT look at the 4 hr result for screening!
2. Look at 8 hr result

→ IF cortisol >1.4 µg/dL

→ Consistent w/ Cushing's syndrome



LDDST: *Differentiation* Interpretation

(USE YOUR LAB'S NUMBERS!)

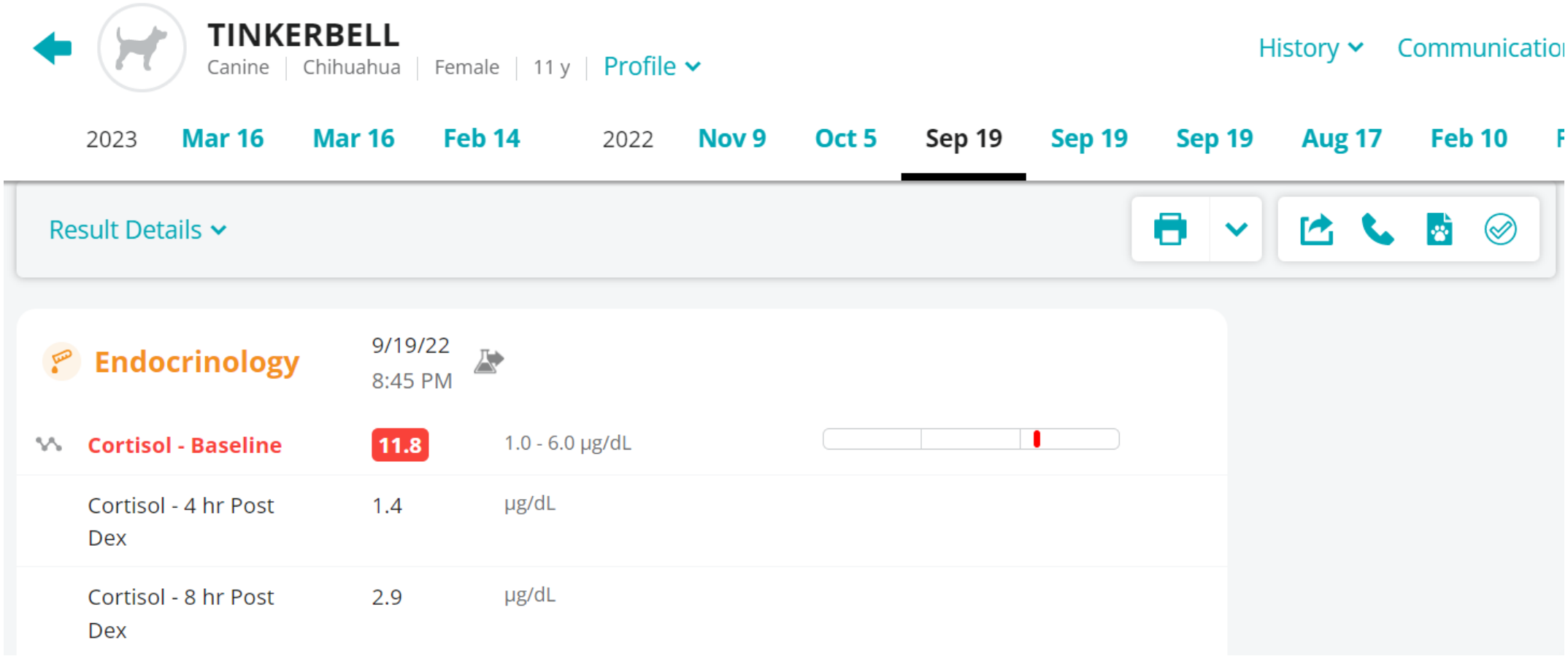
PDH if: **4 hr < 1.4 µg/dL OR**

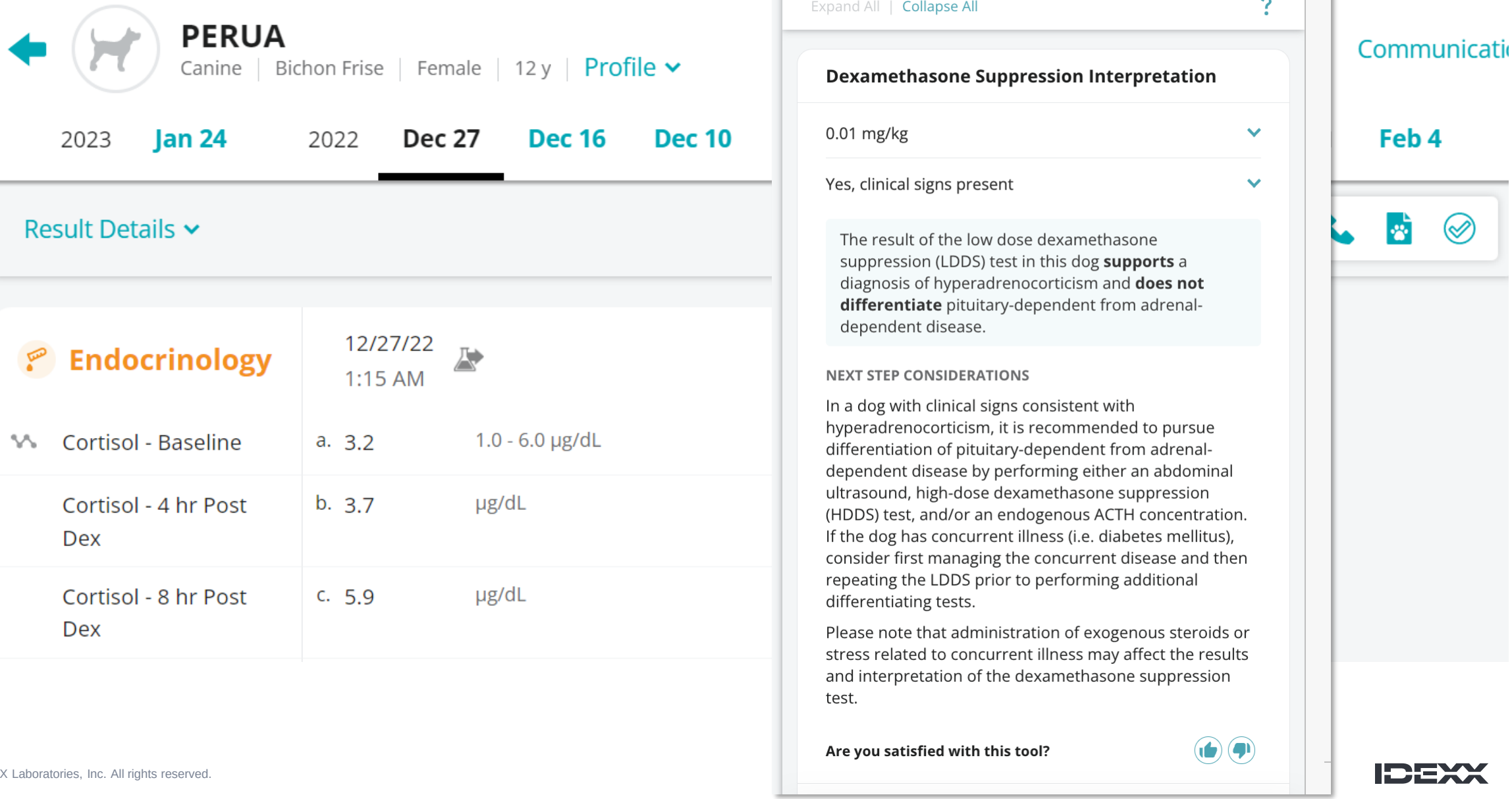
4 hr < ½ baseline OR

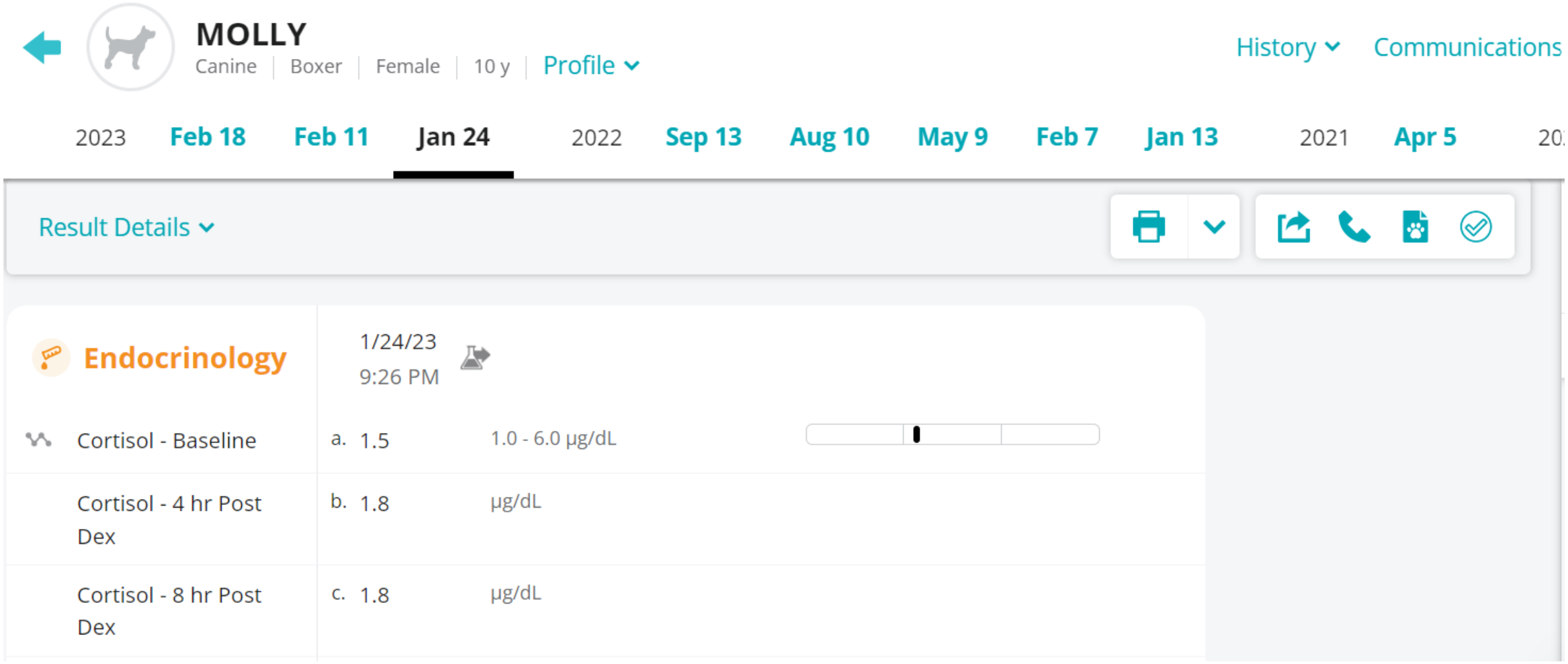
8 hr < ½ baseline

35% of PDH dogs DO NOT FIT THESE CRITERIA!!!

CANNOT RULE-OUT PDH BASED ON LDDST!!!







Thank you!

Insulin protocols for DKA in dogs

- Regular insulin CRI
- Regular insulin intermittent IM injection
  - 0.2 U/kg once then 0.1 U/kg q1h
- Lispro insulin? Longer acting insulins (e.g., glargine)?

Add 1-2 U/kg to 240 ml saline
BG >400 = 20 ml/h, 0% dextrose
BG 250-400 = 10 ml/h, 0% dextrose
BG 150-250 = 5 ml/h, 2.5% dextrose
BG 80-150 = 0 ml/h, 5.0% dextrose
BG <80 = 0 ml/h, 5.0% dextrose, bolus 1 mg/kg 50% dextrose

In clinic testing for pancreatitis

- **SNAP cPL**
  - ***Screening* test: negative result rules OUT pancreatitis**
  - **Positive result *could* be pancreatitis – must confirm.**

- **Catalyst® pancreatic lipase**
  - **Excellent correlation with Spec cPL/fPL and cPLI/fPL**
  - **Specific for *pancreatic* lipase**
  - **Quantitative result in minutes**

Treat DKA and pancreatitis simultaneously

- LRs: restore volume, hydration, keep up with ongoing losses, provide maintenance (avoid volume overload)
  - Death due to hypovolemia, acidosis, multiple organ failure
- Regular insulin
  - Lispro, others?
- Analgesia in *all*: buprenorphine, methadone, fentanyl…
- Maropitant 1 mg/kg SC q24h if vomiting

Do I have to use regular insulin CRI* for DKA?

Not necessarily…

*constant rate infusion

Crisis over. I still think this diabetic dog has Cushing's syndrome. How can I prove it?

This is tricky but we have some tips…

(first tip is…ABSOLUTELY NOT NOW!!!)

Does your diabetic dog also have Cushing's?

- Cushing's most common cause of insulin resistance in dogs
- Suspect concurrent Cushing's syndrome when:
  - Lack of response to or short/variable duration of insulin
  - PU/PD (USG <1.020) despite decent glucose regulation
  - Hypertriglyceridemia
  - Panting, derm changes, pot belly, hepatomegaly…

Cushing’s testing in known diabetic

- Wait ≈2-4 wk after start of DM treatment
  - False positives if screen for Cushing’s at time of DM dx (stress)
- When weight loss stops
- LDDST if dog stable
- ACTH stim if must screen unstable/unregulated dog
  - More specific – fewer false positives
  - Consider positive with post-ACTH cortisol >?

You Suspect Cushing’s syndrome in a Diabetic

Should I decrease insulin dose when I start trilostane?

In most cases no.

Changing the script.

You’re treating a dog for Cushing’s syndrome.
Cortisol levels look good.
Still pu/pd, lethargic...

Could it also be a diabetic?

Hypersomatotropism (Acromegaly)

- Pituitary adenoma secreting excess growth hormone
- Growth hormone (diabetogenic) converted to IGF-1 (anabolic) in liver, requires insulin
- Clinical signs due to resulting insulin resistance and tissue growth
    - ALIVE defines insulin resistance as varying degrees of interference with insulin action, not specific dose
- Prevalence 25% in diabetic cats

Insulin resistence (>10 U/injection)	Growth hormone excess
Extreme polyphagia	Respiratory stridor (50%)
Pu/pd	Prognathous inferior
Weight gain	Broad face
Lack of weight loss	Large feet
	HCM

Screen

- IGF-1 (insulin-like growth factor 1) 4-8 weeks after insulin therapy
  - Requires insulin to be produced
  - False negative possible in newly diagnosed pre insulin-treated diabetics

Confirm

- Increased IFG-1
- Pituitary mass on CT/MRI

Treating hypersomatotropism

- Treatment
  - Stereotactic radiation
  - Hypophysectomy – best chance for diabetic remission (70-92%)
    - T4, hydrocortisone, DDAVP post-op
  - Pasireotide LAR 6-8 mg/kg monthly SC (somatostatin analog)
  - Cabergoline 10 mg/kg q48h (D2 dopamine agonist)
  - Increase insulin, some plateau above 10-15 U/injection