Recommendations for the Diagnosis and Treatment of Equine Metabolic Syndrome (EMS)

2016

EQUINE ENDOCRINOLOGY GROUP

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Recommendations for the Diagnosis and Treatment of Equine Metabolic Syndrome (EMS)

June 2016

Prepared by the EMS Working Group
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Introduction

Equine metabolic syndrome (EMS), which is characterized by insulin dysregulation, abnormal adipose distribution, and a high risk for laminitis, results from an interaction between genetics and environment. The risk of laminitis in the individual animal therefore depends on the relative weighting of genetic and environmental influences. We can identify high-genetic risk animals that develop EMS with only mild environmental influences, and early detection is essential in these animals. Other horses have a lower genetic influence, but can develop EMS through exposure to improper environments (diets that provide more calories than an animal requires and are high in non-structural carbohydrates). It might therefore be assumed that any horse can develop EMS if pushed far enough in the wrong direction by improper management and exposure to environmental factors. Epigenetic influences on gene expression might also further the development of EMS.

The Equine Endocrinology Group (EEG) is composed of experts in the field of equine endocrinology who provide advice in the form of written guidelines to help veterinary practitioners diagnose and manage equine endocrine disorders. Guidelines are updated every two years or when new information becomes available, and can be found on the EEG web site: http://sites.tufts.edu/equineendogroup.

Table 1 - Definition of Terms

Terms	
Insulin dysregulation (ID)	Any combination of fasting hyperinsulinemia, postprandial hyperinsulinemia (response to oral sugar test or consumed feeds), or tissue insulin resistance (IR).
Equine metabolic syndrome (EMS)	A clinical syndrome associated with an increased risk of laminitis that includes insulin dysregulation and any combination of increased generalized or regional adiposity, weight loss resistance, dyslipidemia, and altered adipokine concentrations.

Figure 1 - **Algorithm for the diagnosis and management of EMS (June 2016)**

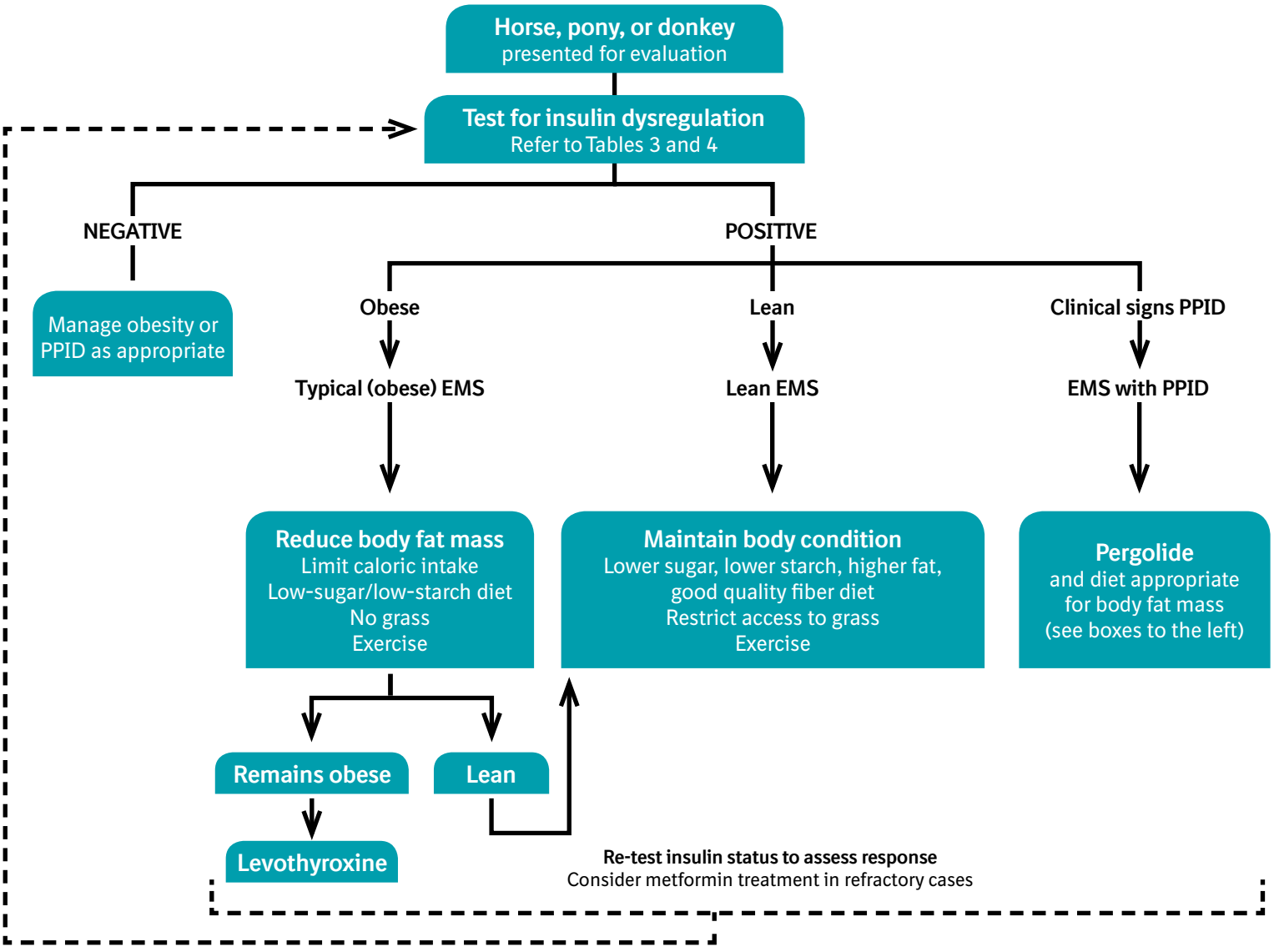
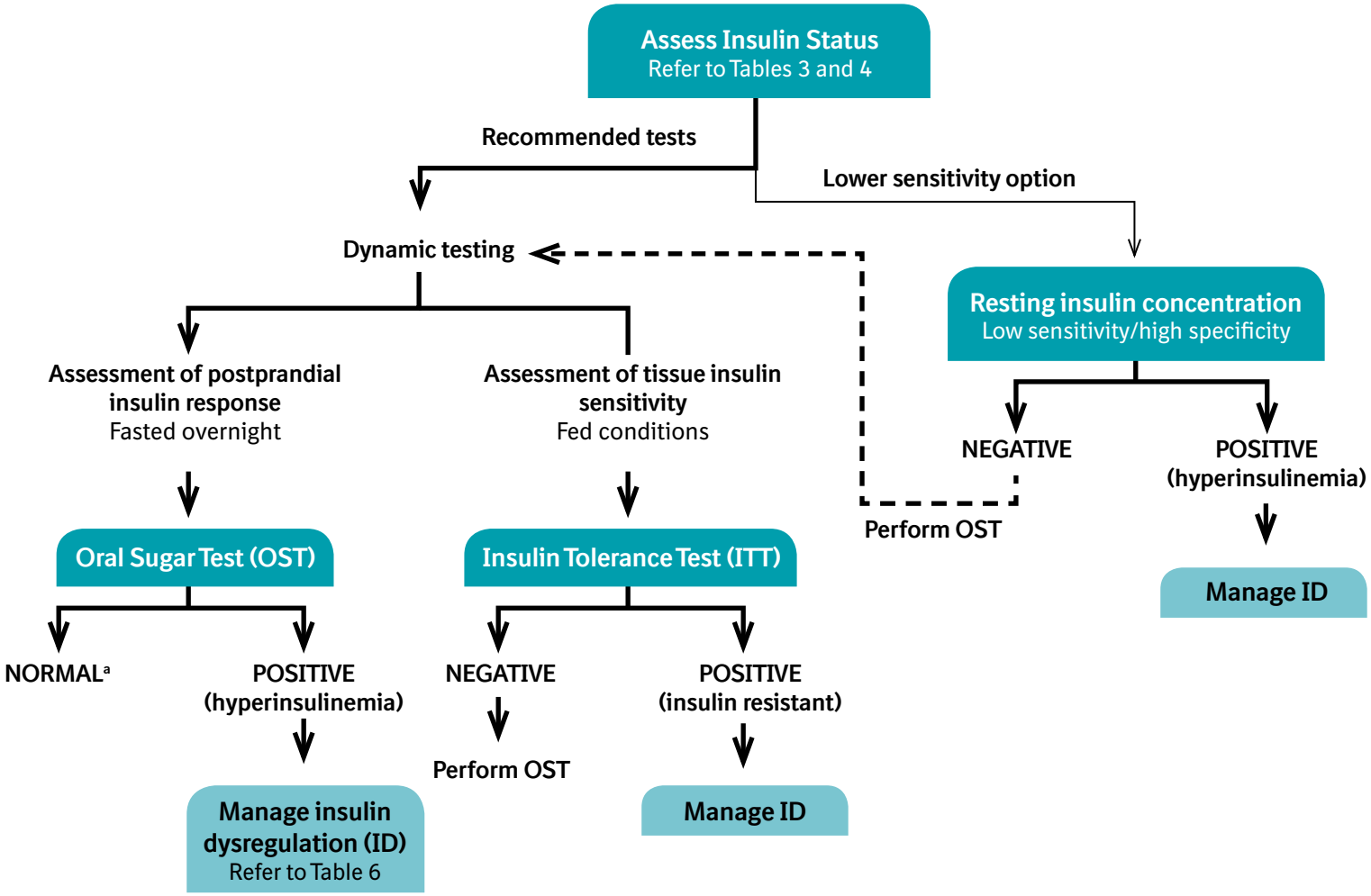


Figure 2 - **Algorithm for detection of insulin dysregulation (June 2016)**



[a] Consider re-testing in 3-6 months if other signs of EMS are present

Table 2 - Clinical presentation of equine metabolic syndrome

Equine Metabolic Syndrome (EMS)		
SIGNALMENT	**CLINICAL FEATURES**	
OBESE (TYPICAL) MANIFESTATION OF EMS		
Genetic risk is implied by certain breeds having higher EMS prevalence Examples of higher genetic risk[a] breeds: Pony breeds Andalusians (PRE) Morgans Paso Finos Miniature horses Saddlebreds Warmbloods Uncertain genetic risk: Donkeys[b]	*Some or all of the following may be present* Weight loss resistance ('Easy keeper'/'Good Doer') Laminitis Cresty neck Subcutaneous adipose deposits Clinical problems may be historical or current	
LEAN MANIFESTATION OF EMS		
Genetic risk horse kept in controlled environment	Laminitis (subclinical or clinical) only	
EMS with PITUITARY PARS INTERMEDIA DYSFUNCTION (PPID)		
EMS may be historical Genetic risk horse that develops PPID (exacerbates insulin dysregulation)	**Clinical signs of EMS** (current problem) Regional adiposity and/or obesity Laminitis	**No clinical signs of EMS currently** (historical problem) Lean/thin at present Laminitis
OTHER POTENTIALLY ASSOCIATED FACTORS		
Diabetes mellitus, critical care metabolic derangements, equine hyperlipemia, infertility, colic caused by a pedunculated lipoma, and preputial/mammary gland edema		

[a] These breeds are overrepresented in surveys of horses with endocrine disease, which suggests a genetic predisposition, but further evidence has not been provided to date.

[b] Equine metabolic syndrome is poorly characterized in donkeys because reference intervals for insulin tests are still being determined.

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Table 3 - Diagnostic testing: Resting insulin concentrations

Resting insulin concentration

Uses: Only use for identifying more severely affected animal (test has low sensitivity/high specificity)
Convenience sampling
Update: Fasting samples no longer recommended

Procedure

After hay (no grain)	**While on pasture**
Do not feed grain within 4 hours Collect into serum or EDTA tube (check with laboratory)	Used to assess insulin concentrations during grazing (assessment of current management)

Assays used[a]

Results must be interpreted in the context of the insulin assay used (chemiluminescent assay, radioimmunoassay, or ELISA)

Results

Results	Interpretation[b]	Recommendation
< 20 µU/mL	Non-diagnostic	Dynamic test recommended to better assess
20-50 µU/mL	ID suspect	
> 50 µU/mL	Insulin dysregulation	Proceed with ID management

[a] Assay should be validated for use with equine samples

[b] Quality of forage can vary and affect results; cut-off values are for low non-structural carbohydrate hay

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Table 4 - Dynamic insulin tests

Dynamic Insulin Testing			
	Assessment of postprandial insulin response		Insulin sensitivity
	Oral Sugar Test [a,1]	**In-feed Oral Glucose Test** [2]	**Insulin Tolerance Test** [b,3]
Procedure	Fast 3 -8 hours Administer 0.15 mL/kg bwt[a] corn syrup orally via dose syringe Collect blood at 60 and 90 minutes Measure insulin and glucose	Fast overnight Administer 0.5 or 1.0 g/kg bwt dextrose powder in non-glycemic feed Collect blood at 2 hours Measure insulin and glucose	Fed conditions (do not fast) Collect blood at time 0 and administer 0.10 IU/kg bwt regular (soluble) insulin intravenously Collect blood at 30 minutes Measure glucose
Interpretation	Insulin response: > 45 µU/mL positive Assess glucose to detect diabetes mellitus (rare)	Insulin response: > 68 µU/mL[c] for 0.5 g/kg bwt > 85 µU/mL[c] for 1.0 g/kg bwt Also measure glucose to ensure that the meal was consumed and to detect diabetes mellitus (rare)	Glucose response: < 50% decrease from baseline is consistent with insulin resistance[d]

[a] Higher amounts of corn syrup (up to 0.45 mL/kg) may provide greater sensitivity, but cut-off values are not available at this time

[b] A combined glucose-insulin test[4] can be used as an alternative

[c] Measured by chemiluminescent assay

[d] Note that hypoglycemia can develop when performing this test

[1] Schuver A, Frank N, Chameroy KA, et al. Assessment of insulin and glucose dynamics by using an oral sugar test in horses. *J Equine Vet Sci* 2014;34:465-470.

[2] Smith S, Harris PA, Menzies-Gow NJ. Comparison of the in-feed glucose test and the oral sugar test. *Equine Vet J* 2016;48:224-227.

[3] Bertin FR, Sojka-Kritchevsky JE. Comparison of a 2-step insulin-response test to conventional insulin-sensitivity testing in horses. *Domest Anim Endocrinol* 2013;44:19-25.

[4] Eiler H, Frank N, Andrews FM, et al. Physiologic assessment of blood glucose homeostasis via combined intravenous glucose and insulin testing in horses. *Am J Vet Res* 2005;66:1598-1604.

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Table 5 - Additional tests for assessment of horses with equine metabolic syndrome

Test	Procedure	Interpretation
High molecular weight (HMW) adiponectin Not currently available in USA Offered in United Kingdom[a]	Collect blood in serum tube; chill on ice and keep refrigerated	Values < 3.2 ug/mL consistent with metabolic derangement in adipose tissues and increased risk of laminitis.[1]
Leptin Available in USA[b]	Collect blood in serum or EDTA tube; keep refrigerated	Consult reference interval provided by laboratory. Higher leptin concentrations are associated with increased adiposity and metabolic derangement in adipose tissues. Useful for providing evidence of increased internal adiposity. This hormone is more directly associated with obesity than ID.[1,2]
Triglyceride concentrations Available from most clinical pathology laboratories	Collect blood in serum tube	Consult reference interval for laboratory. Hypertriglyceridemia associated with ID and obesity; and exacerbated by negative energy balance. Hypertriglyceridemia is a predictor of laminitis risk in ponies, with cut-off values of 57 and 94 mg/dL previously reported.[3,4]

Potential Future Tests

Glucose-dependent insulinotropic peptide (GIP) concentrations, active glucagon-like peptide-1 (GLP-1) concentrations, C-peptide concentrations, arginine stimulation test, and octreotide response test

[a] Liphook Equine Hospital (http://liphookequinehospital.co.uk/equine-laboratory/)

[b] Animal Health Diagnostic Center at Cornell University (https://ahdc.vet.cornell.edu/)

[1] Menzies-Gow NJ, Harris PA, Elliott J. Prospective cohort study evaluating risk factors for the development of pasture-associated laminitis in the UK. *Equine Vet J* 2016.

[2] Bamford NJ, Potter SJ, Baskerville CL, et al. Effect of increased adiposity on insulin sensitivity and adipokine concentrations in different equine breeds adapted to cereal-rich or fat-rich meals. *Vet J* 2016; 14:14-20.

[3] Carter RA, Treiber KH, Geor RJ, et al. Prediction of incipient pasture-associated laminitis from hyperinsulinaemia, hyperleptinaemia and generalised and localised obesity in a cohort of ponies. *Equine Vet J* 2009;41:171-178.

[4] Treiber KH, Kronfeld DS, Hess TM, et al. Evaluation of genetic and metabolic predispositions and nutritional risk factors for pasture-associated laminitis in ponies. *J Am Vet Med Assoc* 2006;228:1538-1545.

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Table 6 - Management recommendations for equine metabolic syndrome

Management and monitoring of EMS	
Obese (typical) EMS BCS 6-9/9	**Initial diet** Do not feed grain For weight loss, feed 1.5% of current body weight in hay (as-fed) daily for 30 days Reassess body weight every 30 days using a weight scale or weight tape and gradually lower to a minimum of 1.2% of body weight as-fed if weight loss resistance. House in a dry-lot or small paddock with a companion. Non-structural carbohydrate (NSC) analysis of hay recommended if severe ID. Soak hay in cold water for 60 minutes before feeding to lower the sugar content.[a] Provide mineral/vitamin/protein ration balancer. Take precautions to limit stereotypic behavior by using slow feeders and monitor horses housed in stalls for consumption of bedding materials. Turnout on pasture strongly discouraged until weight loss achieved. **Maintenance diet** Do not feed grain. Maintain on calculated hay amount until reach body condition 5/9. Improvement in the values obtained from the same test(s) used to diagnose EMS (OST, ITT, HMW adiponectin, or leptin concentrations) is expected. Soak hay. Provide mineral/vitamin/protein ration balancer. Turnout decision based upon follow-up testing of postprandial insulin response. **Exercise**[b] Daily exercise: Trotting, work on hills. Not recommended for horses with active laminitis. **Medical therapy** *High-dose levothyroxine* Indications: For cases with weight loss resistance (no response after a minimum of 30 days on weight loss diet) or for accelerated management of obesity in acute laminitis cases. Available in the USA, high cost restricts use in the UK or Europe. Administer levothyroxine at a high dose of 0.1 mg/kg (48 mg or 4 teaspoons for a 500-kg horse) daily in the feed or by mouth while also controlling caloric intake. Gradually reduce the dose and discontinue treatment after weight loss achieved or 3-6 months later. *Metformin hydrochloride* Indications: When poor owner compliance with dietary recommendations; for the first two weeks that the horse is transitioned to pasture, for animals with persistent hyperinsulinemia. Administer 30 mg/kg metformin hydrochloride in the feed or by mouth 30 minutes prior to feeding or turnout; up to 3 times daily.

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Table 6 - Management recommendations for equine metabolic syndrome (cont.)

Management and monitoring of EMS	
Lean EMS BCS 4-5/9	Diet: Maintain on low-glycemic diet, with stringency of measures dependent on postprandial insulin response. Analyze NSC content of hay if severely affected. Provide diet with low-NSC, high-fat, and add calories in the form of high-quality fiber content such as beet pulp, and soy hulls. Provide mineral/vitamin/protein ration balancer. Exercise: As above Medical: Levothyroxine not recommended, as weight loss is not required.
EMS with PPID	Follow appropriate recommendations from above, depending upon body condition score. Medical: Administer pergolide (Prascend® (pergolide tablets); Boehringer-Ingelheim Vetmedica, Inc.); refer to 2015 EEG Recommendations on PPID.

[a] Acknowledging that this will not reliably lower the NSC content to <10% in all hays[1]

[b] There is limited evidence of direct beneficial effects of exercise on obesity and ID.

[1] Longland AC, Barfoot C, Harris PA. Effects of soaking on the water-soluble carbohydrate and crude protein content of hay. *Vet Rec* 2011;168:618.

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Table 7 - Consideration of pituitary pars intermedia dysfunction (Cushing's disease) status

Consideration	
Age	EMS affects horses across a wide range of ages. PPID is an increasingly common comorbidity as horses age above 10 years and may occur with greater frequency in equids affected by EMS.[a]
Impact on ID	PPID is an exacerbating factor for ID because of the effects of endocrine imbalances on tissues.
Diagnostic testing	Refer to 2015 EEG recommendations for diagnosis and management of PPID. Early affected horses should undergo thyrotropin-releasing hormone (TRH) stimulation testing. Plasma ACTH concentrations can be measured. Detection of a high ACTH concentration confirms the diagnosis of PPID, but horses with negative results should be assessed with the TRH stimulation test.
Management	*Diet:* Based upon the postprandial insulin response. An OST or oral glucose test is recommended for all horses diagnosed with PPID. *Exercise:* Refer to Table 6. *Medical:* Administer pergolide (Prascend® (pergolide tablets); Boehringer-Ingelheim Vetmedica, Inc.) *Comorbidities:* May require management of other medical problems related to PPID and age, including bacterial infections, dental disease, organ dysfunction, and parasitism. *Critical illness:* Insulin dysregulation and PPID are complicating factors in patients with critical illness and may predispose affected patients to hyperglycemia and hypertriglyceridemia. Endocrine system decompensation may adversely affect treatment outcomes.

[a] There are no published research studies that establish a causal relationship between EMS and PPID.

Disclosures

Andy Durham and Lisa Tadros are affiliated with the Liphook Equine Hospital and the Diagnostic Center for Population and Animal Health (DCPAH) at Michigan State University, respectively and both institutions offer endocrine testing.

Boehringer Ingelheim Vetmedica, Inc. facilitates the development of EEG guidelines by supporting travel expenses for participants, but does not influence the recommendations made by the group.