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DIAGNOSIS OF INSULIN RESISTANCE AND PPID

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There are numerous opinions of how to best obtain a diagnosis for IR and PPID. This presentation is a combination of what is in the literature and what the Equine Cushing’s and Insulin Resistance Group has found to work for a practical and effective, on-the-ground experience.

WHY TEST AT ALL?

Even with animals presenting with classical symptoms, it is still a good idea to test, because a baseline can then be established for comparison against different therapies tried. Testing also allows one to assess progress.

EVALUATION OF TESTS

Four areas will help evaluate whether the test is likely to give a valid diagnosis:

1. **Sensitivity** is the ability to detect the problem. A highly sensitive test gives few false negatives; however, the more sensitive the test, the more it MAY increase the chance for a false positive.

2. **Specificity** is the ability to diagnose a particular issue. With greater specificity one is less likely to get the wrong diagnosis. High specificity means few false positives.

3. **The Cost:Benefit ratio** is a valid tool with which to assess the benefit of extra cost or steps in a more complicated test procedure over another. One test may be slightly better at getting a diagnosis than another, but needs hours of time and multiple samples. In most cases of PPID and IR tests, the benefit derived is not worth the extra cost.

4. **Feasibility** weighs the cost and time investment in a testing protocol, such as moving the horse long distances to get the tests done.

Cost/Benefit and Feasibility are very valid concerns for the owner.

TOTAL PREDICTIVE POWER

Total Predictive Power is how much one can rely on a test result, calculated by:

\[
\text{TP} + \frac{\text{TN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}}
\]

\[
\text{TP} = \text{true positive}
\]

\[
\text{TN} = \text{true negative}
\]

\[
\text{FP} = \text{false positive}
\]

\[
\text{FN} = \text{false negative}
\]

By calculating the Total Predictive Power of any test, one can achieve a percentage rating to assess whether or not the right diagnosis can be made.
**DIAGNOSING INSULIN RESISTANCE**

Insulin resistance (IR) is the failure of insulin sensitive cells to respond to “normal” levels of insulin.

There are many controversies over how best to test for IR in equines. There is a dynamic interaction between glucose and insulin that changes over the course of the day. Insulin levels change when the horse eats, sleeps or exercises. A normal level will depend on conditions of the test.

Intravenous testing involving multiple samples over a prolonged period of time using the **Minimal Model intravenous testing**. This protocol is universally recognized as the most appropriate and accurate protocol for detecting insulin resistance in horses. Minimal Model testing calculates four different components of the response to intravenous glucose in a Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT) and involves as many as 30 samples for glucose and insulin drawn over a 3 to 4 hour period.

Reference ranges for horses were published in 2005.¹

Other intravenous testing protocols have been suggested but none are more accurate. Minimal Model intravenous testing is therefore the “gold standard” for IR testing in horses.

The **CGIT** is a combined glucose and insulin tolerance test, performed intravenously. This also takes several hours and requires multiple samples, although a shorter version (1 hour) may be used in the field. A catheter is placed. Stress can influence the results, particularly the glucose response.

A 2-step **insulin response test** was recently described. Samples for glucose are taken before and 30 minutes after an injection of insulin. Most horses tolerate it well but there is a risk of hypoglycemia.²

The **Oral Glucose Tolerance Test** uses 15 mL of Karo corn syrup per 100 kg of body weight. Insulin over 60 µIU/mL at 60 or 90 minutes is considered positive. Details of the research behind this test are not yet published. Gastric emptying time could affect this test. It is a likely laminitis risk.

The ECIR Group bases its protocol on the Virginia Polytechnic Institute Pony Field Study³, a year-long field study of 160 crossbred ponies on pasture, using the results from Minimal Model testing and generating “proxies”.

These more simple calculations were based on single samples of insulin and glucose that could mirror the results of the more intensive sampling of Minimal Model testing, resulting in a spectrum of insulin sensitivity from IR to normal:

- **RISQI** is reciprocal of square root of insulin, a measurement of insulin sensitivity.
- **MIRG** is modified insulin:glucose ratio, a measurement of acute insulin response to glucose.

**HOW THE PROXIES RATE IN TOTAL PREDICTIVE POWER**

Specificity is high at 85%. Because it’s a dynamic test, sensitivity is 48 to 50%. Total Predictive Power is fairly high at 78% but, as stated above, it is important to carefully define the conditions of testing when interpreting results.

In the VA Pony Study, none of the ponies were fasted before testing. In the normal group, insulin of ponies on grass was no higher than 12, eating the same pasture that foundered other ponies.

Treiber also looked at a simple G:I ratio to assess insulin sensitivity. Correlation coefficient is virtually the same as for RISQI: G:I = 0.758, RISQI = 0.774.
**LEPTIN**

Leptin is the satiety hormone that tells the horse to slow down or stop eating. IR horses are also leptin resistant and will not stop with free-choice eating. Heavier horses have higher leptin. Leptin levels will change with age, and sudden changes in nutrient requirements such as foaling, or starting an exercise program.

Therefore, the ECIR Group recommends a simple blood draw for serum insulin, glucose and leptin. The horse should not be fasted prior to testing, but fed hay only the night before and day of testing. Understanding the conditions of the test and the use of proxies will determine IR status. To calculate the proxies, the ECIR Group Calculator is available to do the math: [http://www.freil.com/~mlf/IR/ir.html](http://www.freil.com/~mlf/IR/ir.html)

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<thead>
<tr>
<th><strong>ECIR GROUP INC. INSULIN RESISTANCE RANGES</strong></th>
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<tr>
<td><strong>BASED ON VA POLYTECHNIC PONY STUDIES:</strong></td>
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<tr>
<td><strong>Insulin</strong></td>
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<tr>
<td>Normal of 12 +/- 1.1 uIU even on spring grass</td>
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<tr>
<td><strong>Glucose</strong></td>
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<td>Less than 100 mg/dL</td>
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<tr>
<td><strong>Leptin</strong></td>
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<td>Normal = less than 4 ng/mL</td>
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<tr>
<td>Intermediate = 4 to 7 ng/mL</td>
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<td>High = over 7 ng/mL</td>
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<tr>
<td><strong>RISQI</strong></td>
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<tr>
<td>Greater than 0.32 normal</td>
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<tr>
<td>0.22 – 0.32 compensated IR</td>
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<tr>
<td>Less than 0.22 severe IR</td>
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<tr>
<td><strong>MIRG</strong></td>
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<td>Greater than 5.6 = IR</td>
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**DIAGNOSING PPID/EQUINE CUSHING’S DISEASE**

Controversies also exist around best testing to diagnose PPID. There is no perfect test. The gold standard for PPID testing is how well it correlates with pituitary pathology as determined by postmortem examination. This is the only 100% way to accurately assess testing.

Baseline endogenous ACTH and the Dexamethasone Suppression Test (DST) are most frequently used.

**ACTH** requires special handling and shipping on ice. It is the least traumatic to the horse, not dangerous, and easy to pull in the barn. It is just as accurate as DST.

**Dexamethasone Suppression Test** (DST) will suppress cortisol levels in a normal horse. DST is more sensitive giving more positive results; however, it is less specific, resulting in more false positives. DST also carries the risk of inducing laminitis, especially in Insulin Resistant horses. Dexamethasone is labelled identifying this risk.

**TRH Stimulation** is an older test, first introduced to assess the rise in cortisol. It has since been modified to look at ACTH, which is more accurate than looking at cortisol. TRH stimulates ACTH production. The response is much higher in PPID horses.

TRH Stimulation is more sensitive than ACTH testing in picking up early pituitary changes but has a higher false-positive rate. The horse may have a slight hypertrophy of the pituitary but is asymptomatic. Should he be on pergolide?

Significance of early/low grade pituitary changes is currently unknown. Do all progress to PPID? TRH is primarily indicated for horses with borderline ACTH results but suggestive symptoms.
**Domperidone Stimulation** has been correlated with pathological samples. It is perhaps as sensitive as TRH. The drug is administered orally and ACTH tested before and at 4 hours after dosing.

Domperidone Stimulation is less sensitive than TRH stimulation in one study\(^5\)

In both TRH and Domperidone Stimulation, the clinical significance of positive tests in clinically normal horses with minor pituitary changes needs to be investigated.

The ECIR Group recommends *Endogenous ACTH*: a single blood draw to measure the level of endogenous ACTH (adrenocorticotropic hormone) The sample requires special handling for accuracy. As with DST and TRH, there are seasonal fluctuations to consider for diagnosis of PPID.

*For more information see [ecirhorse.org](http://ecirhorse.org)*

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