

DUTCH PLUS™ WITH CORTISOL AWAKENING RESPONSE - PROVIDER INFORMATION SHEET

The **DUTCH Plus™** takes hormone testing to a whole new level



The **DUTCH Plus™** takes hormone testing to a whole new level. In addition to sex hormones and their metabolites, the **DUTCH Complete™** looks at the overall diurnal pattern of free cortisol, and the total and distribution of cortisol metabolites. The **DUTCH Plus™** adds the Cortisol Awakening Response (CAR) to bring another important piece of the HPA-axis into focus.

What is the Cortisol Awakening Response and how do we test for it?

When we open our eyes upon waking, cortisol levels naturally begin to rise by an average of 50%. 30 minutes after waking, cortisol levels will still show this sharp increase. By 60 minutes after waking, cortisol levels have peaked and begin to decline. Measuring this rise and fall of cortisol levels at waking can be used as a “mini stress test”. Research shows that the size of this increase correlates with HPA-axis function, even if the sample measurements are all within range. A quick saturation of saliva swabs upon waking, and at 30 and 60 minutes after waking, provide what is required to assess a patient’s Cortisol Awakening Response.

A low or blunted Cortisol Awakening Response

can be a result of an underactive HPA axis, excessive psychological burnout, seasonal affective disorder (SAD), sleep apnea or poor sleep in general, PTSD, chronic fatigue and/or chronic pain. A decreased CAR has also been associated with systemic hypertension, functional GI diseases, postpartum depression, and autoimmune diseases.

An elevated Cortisol Awakening Response

can be a result of an over-reactive HPA axis, ongoing job-related stress (anticipatory stress for the day), glycemic dysregulation, pain (i.e. waking with painful joints or a migraine), and general depression (not SAD). A recent study¹ showed that neither the waking nor post-waking cortisol results correlated to Major Depressive Disorder, but the CAR calculation (the change between the first two samples) did. This measurement of the response to waking has independent clinical value showing dysfunction that may be hidden by current testing options.

What’s Included in the DUTCH Plus™?

The DUTCH Plus™ uses four dried urine samples and five saliva samples. These samples are collected over the course of one day, from waking to bed time.

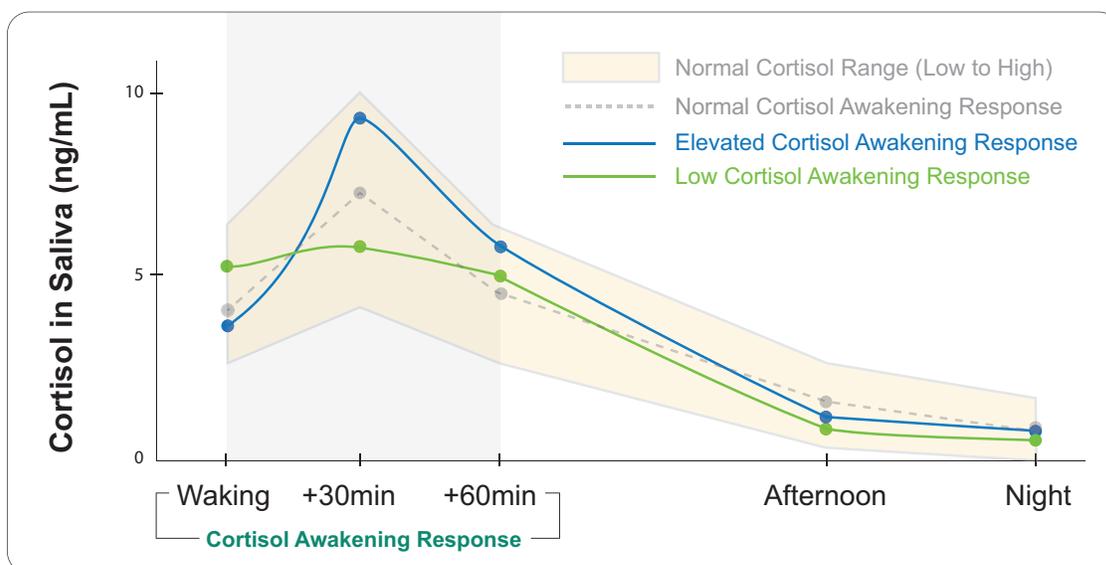


DUTCH PLUS™ WITH CORTISOL AWAKENING RESPONSE - PROVIDER INFORMATION SHEET

The **DUTCH Plus™** report includes: Metabolites of Estrogens (10, including E1, E2, E3, 2-OHE1, 4-OH-E1, 2-OH-E2, 4-OH-E2, 16-OH-E1, 2-methoxy-E1, 2-methoxy-E2), Androgens (8, including Testosterone, DHT and DHEA-S), Progesterone (2), Cortisol (3), Melatonin (6OHMS), 8-OHdG, and OATs (6). The diurnal pattern of Free Cortisol and Cortisone are also provided, including the Cortisol Awakening Response.

What can the *DUTCH Plus™* tell us that the *DUTCH Complete™* and other adrenal tests cannot? Even though a patient may have “normal” free cortisol levels throughout the day, that doesn’t always mean everything is functioning properly. The graph below shows two good examples. A blunted or exaggerated CAR can appear, even when single samples return “normal” results. The HPA axis might not be appropriately responding when faced with a stressor, even when cortisol levels are fluctuating nicely throughout the day. The “stress” of waking allows us to test the HPA axis in a way that has been independently correlated to clinical outcomes and cannot be assessed by other cortisol tests on the market.

Daily Free Cortisol with Cortisol Awakening Response



Why aren't true Cortisol Awakening Response tests readily available? A true CAR assessment requires salivary samples to be collected at the moment of waking, and twice more, at 30 minutes after waking and 60 minutes after waking. These specifically timed collections are difficult and impractical with urine and traditional salivary options. The **DUTCH Plus™** uses specialty, FDA-approved, and patented collection devices called **Salivettes™**. **Salivettes™** are specifically made for testing cortisol when timing needs to be precise and are used in nearly all of the published CAR studies. The small synthetic cotton swab can be quickly saturated with saliva, providing a very fast and simple collection. Unfortunately for labs using saliva to test reproductive hormones, they are not a viable option as the swabs cannot be used when testing progesterone. The **DUTCH Plus™** offers the most accurate salivary cortisol sampling with **Salivette™** collection and analysis using LC-MS/MS. An unparalleled clinical tool is created when combining salivary cortisol with the extensive urine metabolites from **DUTCH**.

References 1. Adam EK, Doane LD, Zinbarg RE, Mineka S, Craske MG, Griffith JW. Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. *Psychoneuroendocrinology*. 2010 Jul;35(6):921-31. 2. Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. *Biol Psychol*. 2009 Mar;80(3):265-78. 3. Clow A, Hucklebridge F, Stalder T, Evans P, Thorn L. The cortisol awakening response: more than a measure of HPA axis function. *Neurosci Biobehav Rev*. 2010 Sep;35(1):97-103. 4. Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): Facts and future directions. *International Journal of Psychophysiology* 2009 Apr, 72(1):67-73. 5. Huber TJ, Issa K, Schik G, Wolf OT. The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. *Psychoneuroendocrinology*. 2006 Aug;31(7):900-4. 6. Jakuszkowiak-Wojten K, Landowski J, Wiglusz MS, Cubala WJ. Cortisol awakening response in drug-naïve panic disorder. *Neuropsychiatr Dis Treat*. 2016 Jun 27;12:1581-5. 7. Roberts AD, Wessely S, Chalder T, Papadopoulos A, Cleare AJ. Salivary cortisol response to awakening in chronic fatigue syndrome. *Br J Psychiatry*. 2004 Feb;184:136-41.





When patients suffer from insomnia, the 5 salivary cortisol measurements on the DUTCH Plus™ may not be enough to assess cortisol's potential role in the sleep disturbances. Salivary measurements typically begin when the patient wakes and rises in the morning. It would be very helpful to also provide cortisol levels in the middle of the night when the patient is struggling to sleep. Determining cortisol's potential role will help the provider treat the patient's insomnia with precision.

The DUTCH Plus™ now offers insight into this question.

Why DUTCH Plus™?

The DUTCH Plus™ offers an evaluation of the Cortisol Awakening Response (CAR) by measuring salivary cortisol upon waking and then again 30 and 60 minutes later (additional measurements are made around dinner and bedtime). Research has shown that this post-waking increase in cortisol (the CAR) is the best way to assess an individual's stress response and HPA-axis function.

What insight does DUTCH Plus™ offer an insomnia case?

- Free cortisol values throughout the day, including at bedtime
 - ◆ A high bedtime sample may hinder sleep
- Overnight melatonin production
 - ◆ Low melatonin production may contribute to insomnia
- Progesterone levels
 - ◆ Particularly in perimenopausal, low progesterone may be associated with poor sleep
- VMA
 - ◆ As the primary metabolite of norepinephrine and epinephrine, high levels may be found in patients in sympathetic overdrive, which may lead to insomnia if persistent at night
- The new Insomnia Cortisol measurement
 - ◆ This new measurement offers valuable additional information about cortisol's potential causal role in sleep disturbances.
 - ◆ Note: while the above markers are included in the DUTCH PLUS, the Insomnia Cortisol measurement is optional and included at an additional charge.