GENOVA DIAGNOSTICS

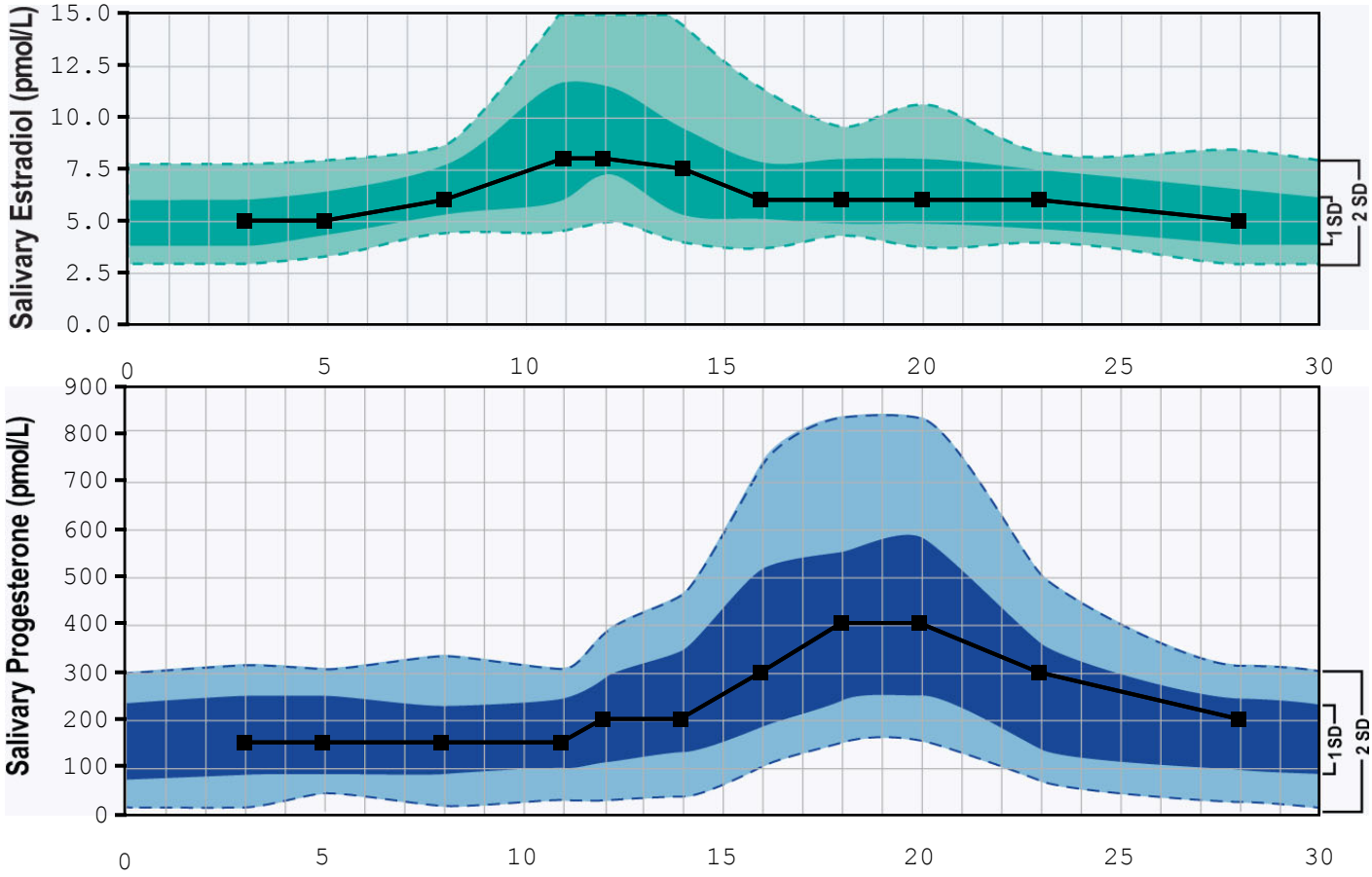
63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Rhythm Plus™

Patient: **PATIENT TEST**

Alec Smart, ND
TEST TEST MD
2141 Rosecrans Ave
East Tower Ste 6100
Silver Spring, MD 00012

Salivary Estradiol & Progesterone Activity plus Testosterone Level



Day of Cycle	3	5	8	11	12	14	16	18	20	23	28	Avg.
Estradiol	5.0	5.0	6.0	8.0	8.0	7.5	6.0	6.0	6.0	6.0	5.0	6.3
Progesterone	150	150	150	150	200	200	300	400	400	300	200	236
P/E2 Ratio	30	30	25	19	25	27	50	67	67	50	40	39

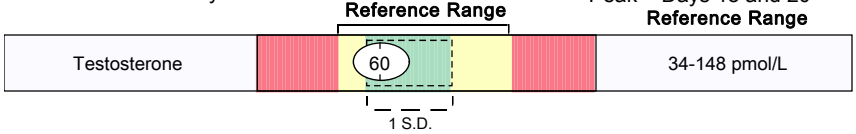
Estradiol	Ref Range
Follicular:	2.8 - 8.8 pmol/L
Peak*:	4.5 - 19.1 pmol/L
Luteal:	2.8 - 8.2 pmol/L
Menopausal:	3.7 - 9.4 pmol/L
Male:	3.1 - 7.4 pmol/L

* Peak = Days 11 and 12

Progesterone	Ref Range
Follicular:	17 - 321 pmol/L
Peak*:	151 - 829 pmol/L
Luteal:	33 - 452 pmol/L
Menopausal:	45 - 370 pmol/L
Male:	31 - 280 pmol/L

* Peak = Days 18 and 20

P/E2 Ratio ♦	Ref Range
Follicular:	10 - 85
Luteal:	8 - 80
Menopausal:	12 - 62



Testosterone	Ref Range
Premenopausal:	34 - 148 pmol/L
Menopausal:	34 - 148 pmol/L
Male:	110 - 513 pmol/L

© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475

Commentary

Methodology: LIA, EIA

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc.
All assays are cleared by the U.S. Food and Drug Administration unless otherwise noted with ♦.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or as treatment recommendations. Diagnosis and treatment decisions are the practitioner's responsibility.

Reference ranges are based on morning collection.

The Reference Range for each day is a statistical interval representing 95% or 2 Standard Deviations (2 S.D.) of the reference population. One Standard Deviation (1 S.D.) is a statistical interval representing 68% of the reference population. Values between 1 and 2 S.D. are not necessarily abnormal. Clinical correlation is suggested.

The first half of the menstrual cycle (Follicular Phase) culminates in an estradiol peak between days 10-14 (in an optimal 28-day cycle – counting from the first day of the last menses). The second half of a 28-day menstrual cycle (Luteal Phase) should demonstrate a progesterone peak between days 18-22, which coincides with a smaller estradiol rise. Ovulation occurs 24-36 hours after the estradiol peak and 10-12 hours after a luteinizing hormone (LH) surge. Alterations in this normal hormonal cycling may be indicative of anovulation or luteal phase defects, which are associated with menstrual bleeding abnormalities. Finally, menstrual cycle lengths often vary from 24-35 days. While the follicular phase may vary in duration, the luteal phase is fixed at 14 days.

Follicular estradiol:
High follicular estradiol levels contribute to menstrual irregularities, breast tenderness, and estrogen-related conditions such as ovarian cysts, endometrial hyperplasia, and uterine fibroids. Low follicular estradiol levels can occur with normal aging, ovarian dysfunction, low body mass, strenuous exercise, chronic stress, or oral contraceptive use.

Follicular progesterone:
Elevated follicular progesterone levels represent HPA axis activity or a persistent corpus luteum from the previous cycle. This finding is not necessarily associated with symptoms, but may accompany prolonged bleeding or polycystic ovary syndrome.
Low follicular progesterone levels are seen in ovarian aging.

Luteal estradiol:
Elevated luteal estradiol levels are seen in decreased estrogen detoxification, high body mass index, hypothyroidism, or transdermal estradiol supplementation. High luteal estradiol contributes to disorders such as PMS, dysmenorrhea, and dysfunctional uterine bleeding. Low luteal estradiol levels on one or more days may result from ovarian insufficiency, low body mass, strenuous exercise, chronic stress, inflammation, or certain medications, including oral contraceptives. Low luteal estradiol is associated with anovulation, scanty periods, or depression-type PMS.

Luteal progesterone:
High luteal progesterone levels are present in some types of PMS, particularly those associated with fatigue, depression and blood sugar dysregulation. Elevated progesterone can also reflect recent transdermal progesterone supplementation.
Low luteal progesterone occurs with luteal defects, anovulation, chronic stress, and certain medications including

Commentary

oral contraceptives. Deficient luteal progesterone is a leading cause of infertility and dysfunctional uterine bleeding, and is relatively common as a woman approaches menopause.
Luteal defects occur when the corpus luteum fails to produce progesterone. In some cases there may be recovery of corpus luteal function with a progesterone level rebound. This situation is relatively common as women age, and is a frequent cause of infertility and recurrent miscarriage. It also contributes to dysfunctional uterine bleeding and PMS.

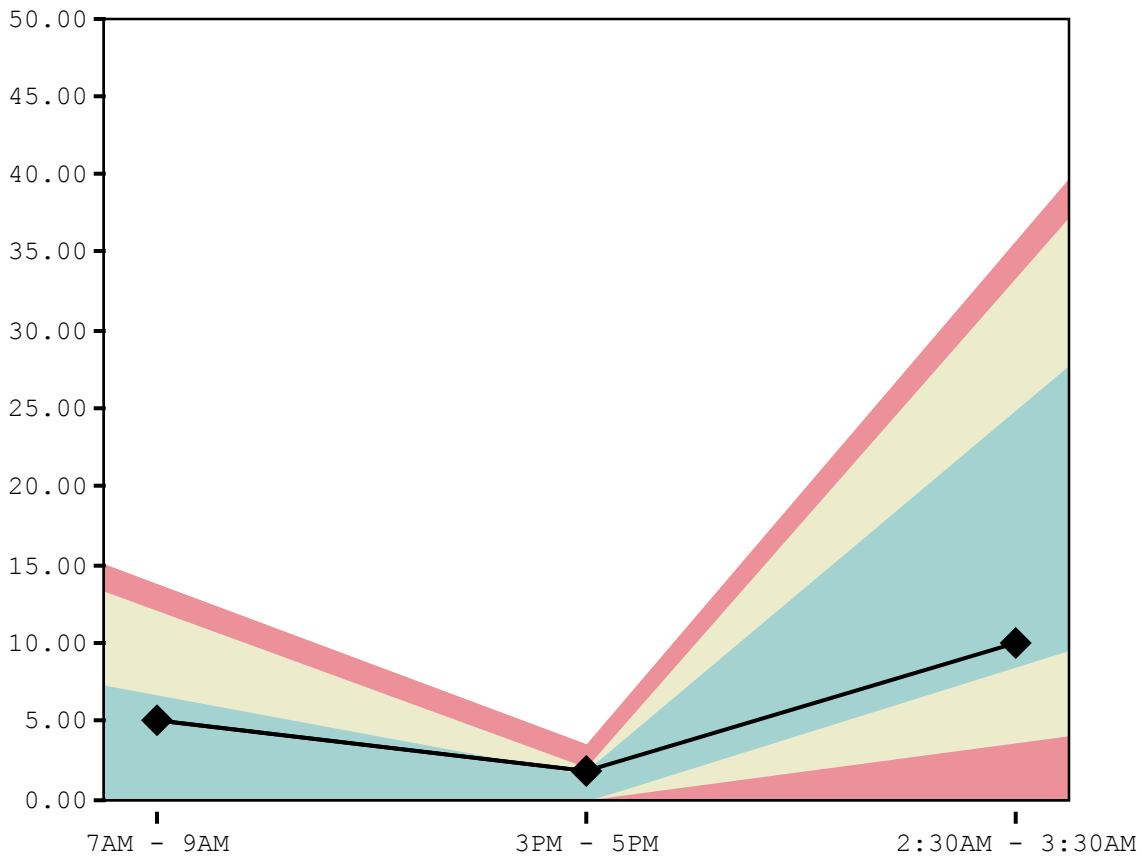
Testosterone:
Normal testosterone levels are important for libido, maintaining lean body mass and bone density. Low testosterone is associated with greater osteoporosis risk, difficulty maintaining lean body mass, decreased libido, effects of aging, and/or ovarian dysfunction.
High testosterone levels in women are seen with polycystic ovary syndrome, acne, hair loss, glucose intolerance, and ovarian dysfunction.

© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475

Comprehensive Melatonin Profile

Methodology: EIA

Salivary Melatonin



Results

	7AM-9AM*	3PM-5PM*	2:30AM - 3:30AM*
Patient Results (pg/mL) >>	**5.00**	**1.80**	**10.00**
Reference Range (pg/mL) *Based on Collection Times	<=12.12	<=1.97	3.71-33.38

Commentary

Please note the reference range for melatonin has been updated due to a change in methodology.

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ◆, the assay has not been cleared by the U.S. Food and Drug Administration.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or as treatment recommendations. Diagnosis and treatment decisions are the practitioner's responsibility.

Melatonin activity is normal throughout the sample period revealing a normal melatonin circadian rhythm. As well as playing a crucial role in sleep-wake cycles, melatonin influences other vital functions, including

© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475

Commentary

cardiovascular and antioxidant protection, endocrine function, immune regulation and body temperature.

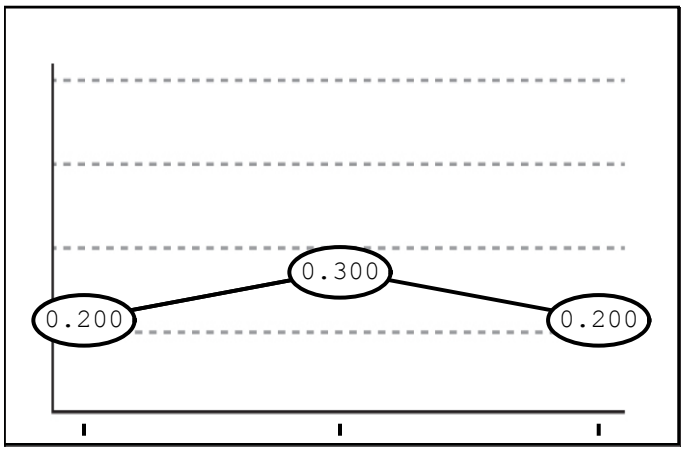
© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475

Cortisol Awakening Response

Methodology: EIA

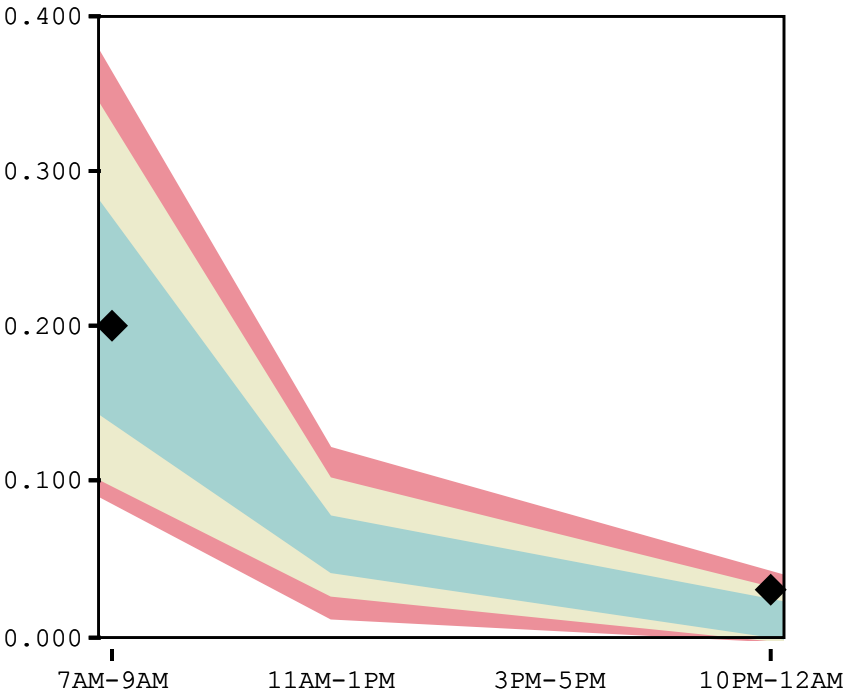
Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response



Percent Increase	50	Expected: >= 50 %

Salivary Cortisol



DHEA

	Reference Range
DHEA 7AM - 9AM♦ (100)	71-640 pg/mL

	Reference Range
DHEA: Cortisol Ratio/10,000♦ (500)	358-2,538

Results

	Waking	30 Minutes	7AM-9AM*	10PM-12AM*
Patient Result (mcg/dL) >>	**0.200**	**0.300**	**0.200**	**0.030**
Reference Range (mcg/dL) *Based on Collection Times	N/A	N/A	0.097-0.337	<=0.034
Actual Collection Time	6:05AM	6:35AM	7:30AM	10:00PM

Commentary

Please note the calculation for CAR has been updated.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or as treatment recommendations. Diagnosis and treatment decisions are the practitioner's responsibility.

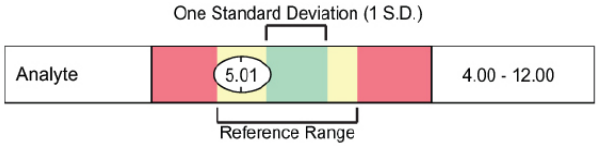
The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. All assay have been cleared by the U.S. Food and Drug Administration, unless otherwise noted with ♦.

© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475

Commentary

The **Reference Range** is a statistical interval representing 95% or 2 Standard Deviations (2 S.D.) of the reference population.

One Standard Deviation (1 S.D.) is a statistical interval representing 68% of the reference population. Values between 1 and 2 S.D. are not necessarily abnormal. Clinical correlation is suggested. (See example below)



Cortisol Awakening Response (CAR)

CAR is calculated by a direct percent increase: difference between 30 minutes and wake, divided by wake, then multiplied by 100. In literature, there are several ways to calculate CAR. Expected increases may differ depending on which calculation is used. Most literature demonstrates an expected increase of greater than 50% as a reflection of HPA axis resiliency.[1]

CAR represents the momentum of rising cortisol levels that begins several hours prior to awakening and an additional transient increase. The initial cortisol rise begins due to ACTH-mediated normal HPA axis activities with the additional CAR increase caused by supra-chiasmic nucleus (SCN) light activation.

CAR reflects a person's ability to cope with anticipated challenges and the perceptions of control around chronic stress. CAR is calculated based on the percent cortisol rise from awakening to 30 minutes. A value of approximately 50% is expected.

Approximately 25% of healthy adults do not mount a CAR, and are termed non-responders. Response is defined as an increase of at least 2.5 nmol/l (0.09 mcg/dL) above individual baseline. Any patient with a result less than this is considered a "non-responder" if sampling was performed correctly and the rest of the diurnal curve shows adequate cortisol response.

- Blunted CAR is seen in clinical burnout, self-reported health problems, early loss experiences, material hardship, depression, PTSD, and amnesia.
- Elevated CAR can be adaptive as a reflection of anticipation for daily stress. It may play a literal role in "preparing for action" by stimulating motor function, immunity responses, and alertness.
- If CAR is abnormal, and the rest of the diurnal pattern is not, then this would imply that a CAR-specific mechanism (SCN-related signaling) is implicated instead of a CRH or ACTH-mediated mechanism. Any abnormality of the hippocampus may blunt the CAR response and not affect the diurnal slope.

- If both the CAR and the diurnal rhythm are abnormal, this may represent a more general HPA dysfunction. It may also be useful to look at DHEA for a complete assessment of the HPA axis.

CAR treatment involves HPA axis and adrenal support using lifestyle modification, nutrition and adaptogens. However, insight into blunted or elevated CAR may help direct additional modalities such as behavioral modification and psychological therapies.

© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475

Commentary

Evening (10:00 PM – 12:00 AM) cortisol levels are a good indication of baseline HPA axis function since they represent the lowest level during the circadian rhythm.

- Elevated levels may be due to stress, exercise, alcohol, and specific lifestyle stressors.
- Elevated evening salivary cortisol is linked to insomnia.
- High evening cortisol levels are also associated with various diseases such as diabetes, cardiovascular disease, hormonally driven cancers, and osteoporosis.

DHEA

DHEA levels peak at around age 25, then decline steadily through the following decades. DHEA can be converted downstream in the steroidogenic pathway to create androgens and estrogens. It has antioxidant and anti-inflammatory properties and can be protective against corticosterone's neurotoxic effects.

- Lower levels of DHEA are seen with advancing age and have been associated with immune dysregulation, cardiovascular disease, arthritis, osteoporosis, insomnia, declining cognition, depression, fatigue, and decreased libido.
- Elevated levels of DHEA may reflect endogenous exposure and supplementation. Other considerations include Polycystic Ovarian Syndrome (PCOS,) adrenal hyperplasia and adrenal tumors.

General recommendations include overall control of the cortisol response, HPA axis support using nutrition, adaptogens, and behavioral modification.

DHEA:Cortisol Ratio

This calculation represents anabolic and catabolic balance. Since DHEA acts not only as an anabolic hormone, but appears to down-regulate the cellular effects of cortisol, this measurement can theoretically enhance the predictive value of HPA axis dysfunction.

- An elevated ratio reflects elevated DHEA levels as compared to cortisol, which favors anabolic activity. Causes of DHEA and cortisol abnormalities should be evaluated.
- A decreased ratio generally reflects a more catabolic state. It is associated with cortisol elevations and HPA-axis imbalances. Causes of DHEA and cortisol abnormalities should be addressed.
- An optimal ratio indicates proper HPA axis homeostasis.

References:

1. Clow A, Thorn L, Evans P. Hucklebridge F. The awakening cortisol response: methodological issues and significance. *Stress.* 2004;7(1):29-37.
2. Stalder T, Kirschbaum C, Kudielka BM, et al. Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrino.* 2016;63:414-432.
3. Wust S, Wolf J, Hellhammer DH, Federenko I, Schommer N, Kirschbaum C. The cortisol awakening response-normal values and confounds. *Noise health.* 2000;2(7):79.
4. Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. *IntJPsychophysiol.* 2009;72(1):67-73.
5. Saxbe DE. A field (researcher's) guide to cortisol: tracking HPA axis functioning in everyday life. *Health Psychol Rev.* 2008;2(2):163-190.

© Genova Diagnostics · A. L. Peace-Brewer, PhD, D(ABMLI), Lab Director · CLIA Lic. #34D0655571 · Medicare Lic. #34-8475