



Utilizing the Rhythm Plus™ Profile

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Technical Issues & Clinical Questions

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- We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



DISCLAIMER: Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.

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The screenshot shows the Genova Diagnostics website with a blue header containing social media icons and navigation links (HOME, CLINICIANS, PATIENTS). The main content area features a webinar announcement for "The Rhythm Plus: Tracking a Full Cycle Through Salivary Hormone Testing" on November 28, 2018, at 12 PM EST. Below this is a "FREE WEBINAR LIVE GDX" badge. Three resource cards are highlighted with red circles: "Getting Started" (with a "NEW USERS" button), "Test Menu" (with a "SEARCH TESTS" button), and "MyGDX Login" (with a "LOG IN" button). At the bottom, an "Online Education" section is also circled in red, featuring a "LEARN NOW" button. A small calendar icon is visible on the left side of the webinar announcement.



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Objectives of This Presentation:

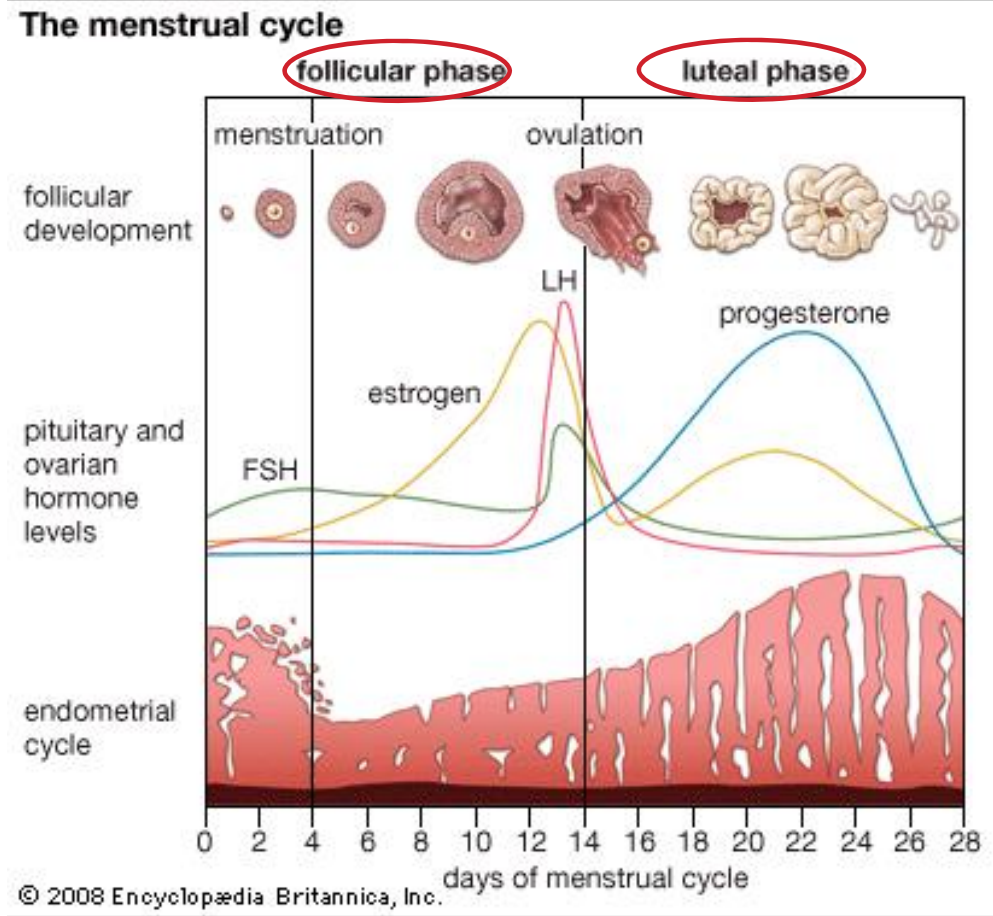
- Assess the menstrual cycle utilizing salivary hormones
- Review the components of the **Rhythm Plus™ Profile**
- Discuss HPA axis insights provided by cortisol and melatonin circadian rhythms
- Discuss Cortisol Awakening Response (CAR) options
- Utilize case studies to demonstrate the clinical utility of the test





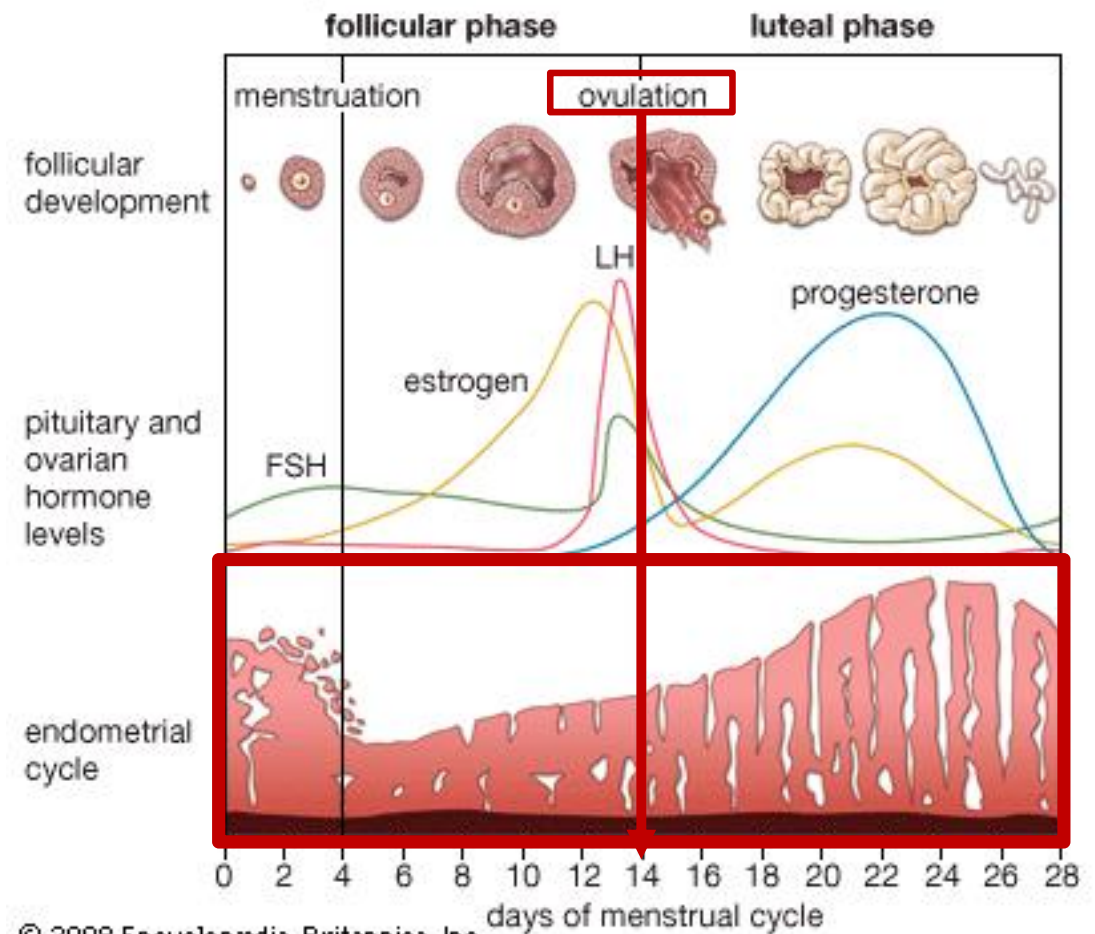
The Menstrual Cycle

- Typical 28 day cycle, comprised of two 14 day phases
- **Follicular Phase-** 14 days, includes a build-up of estradiol followed by a spike *likely* caused by ovulation
- **Luteal Phase-** 14 days, includes a luteal progesterone spike 7 days following the follicular phase spike
- Changes in the length of a cycle are most often the result of a change in the length of the follicular phase



The Menstrual Cycle

The menstrual cycle

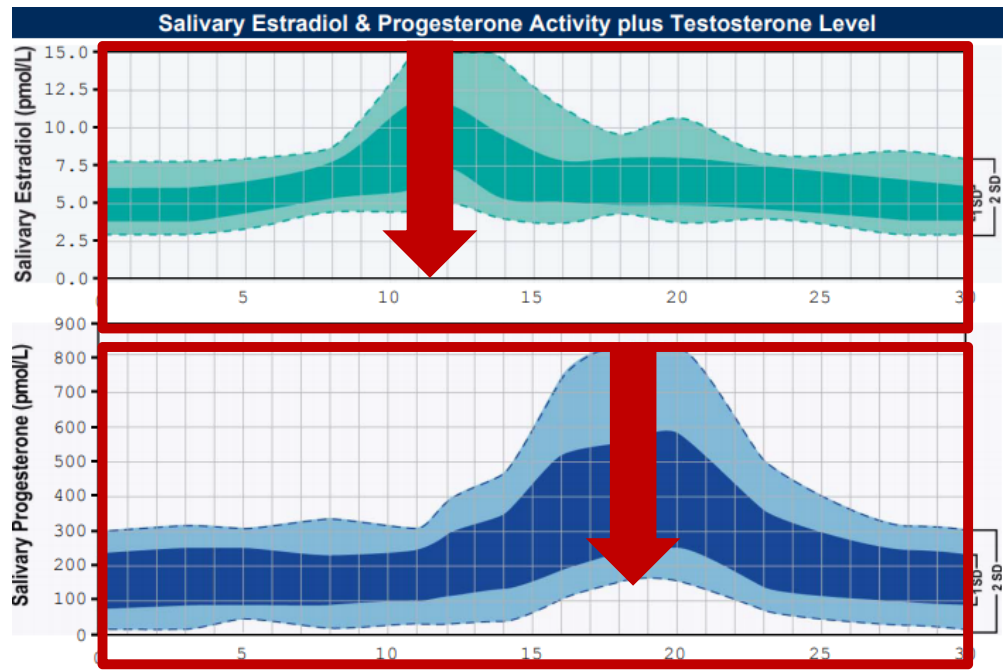
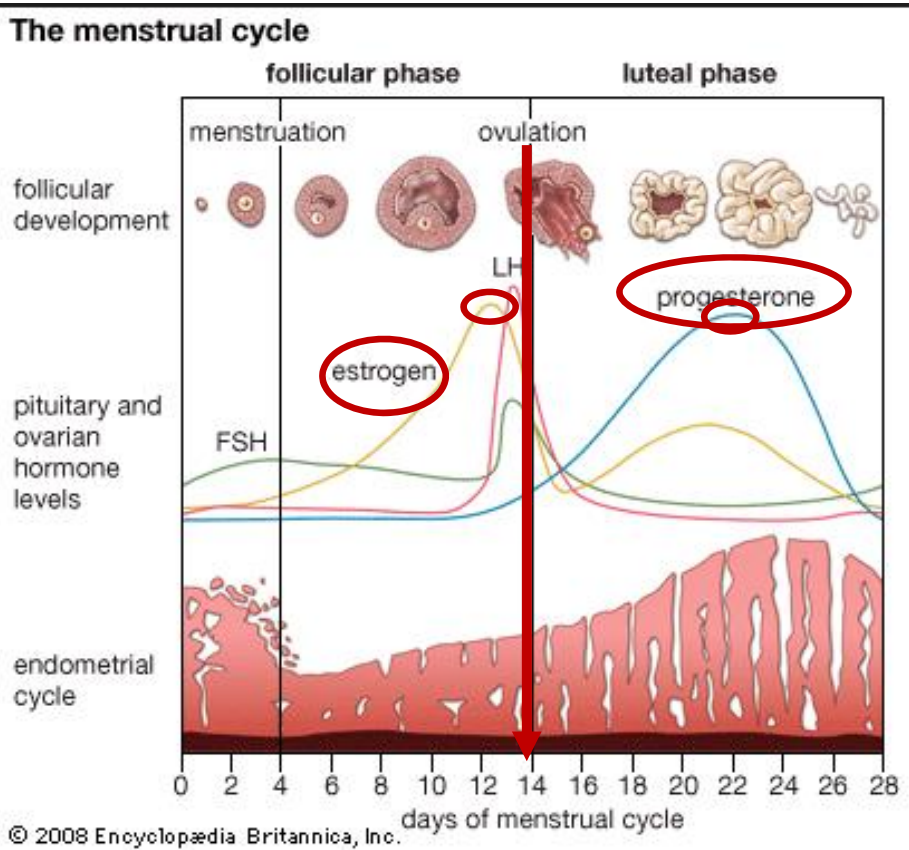


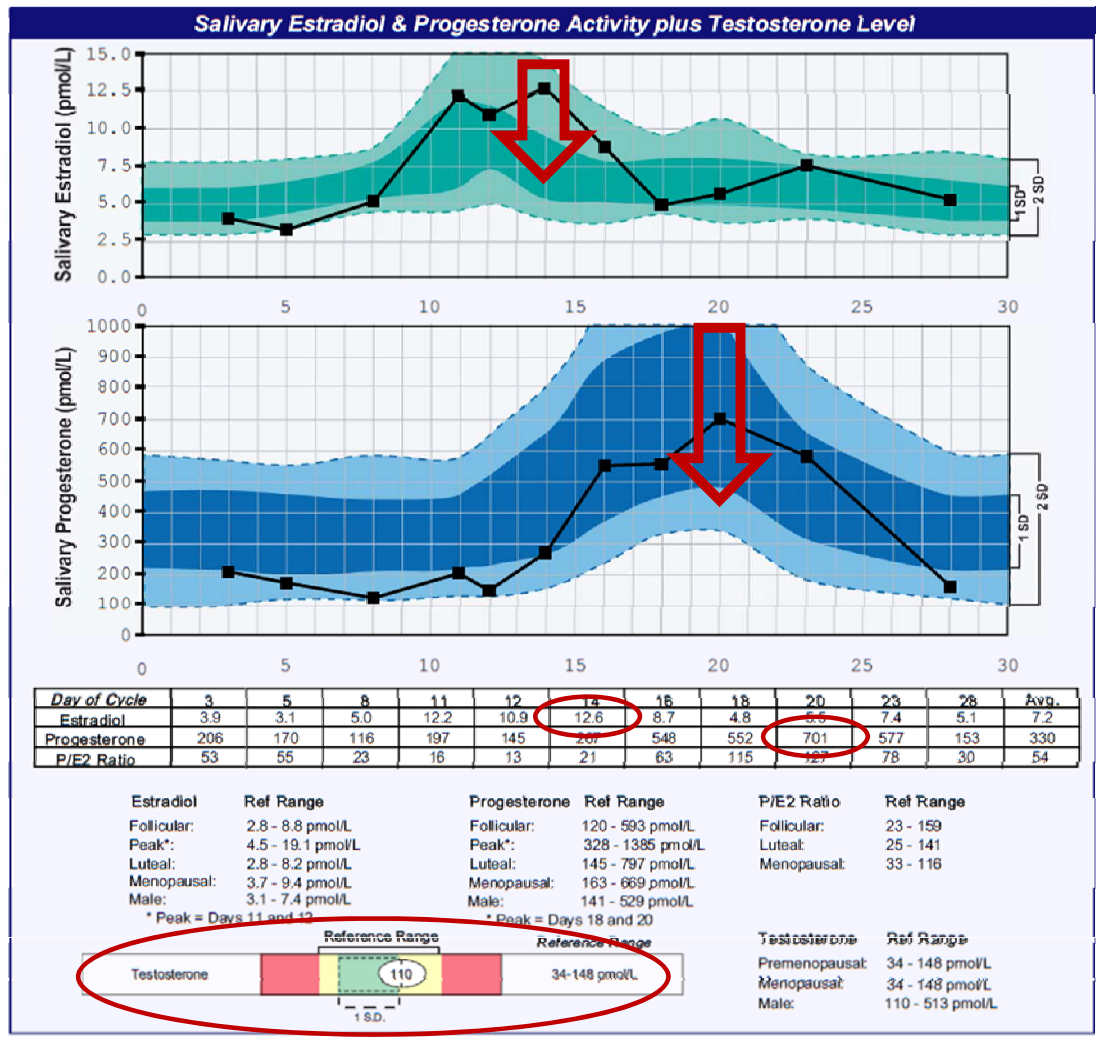
© 2008 Encyclopædia Britannica, Inc.

Image: <https://www.britannica.com/science/menstrual-cycle>



The Menstrual Cycle



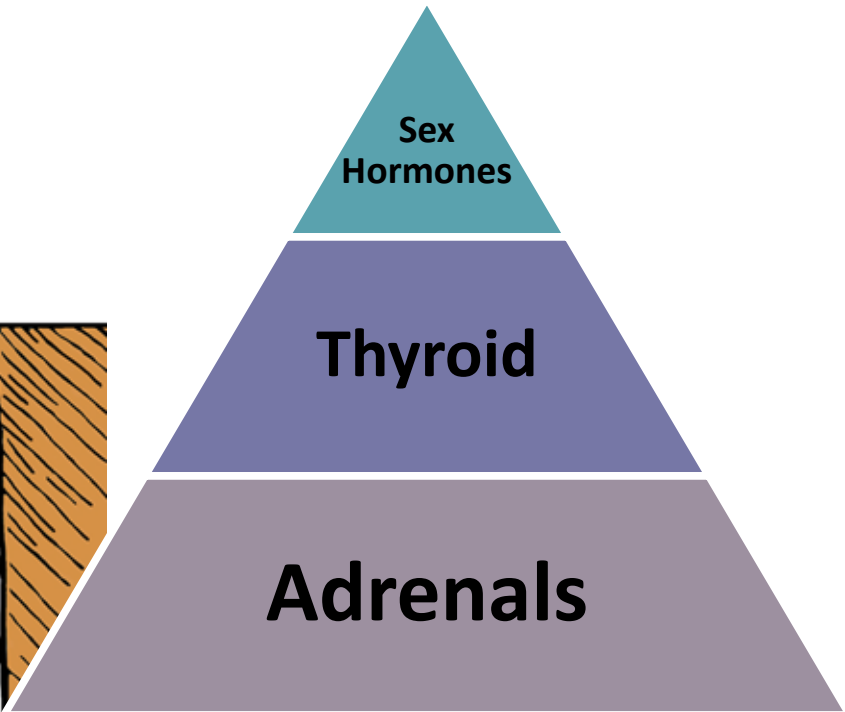
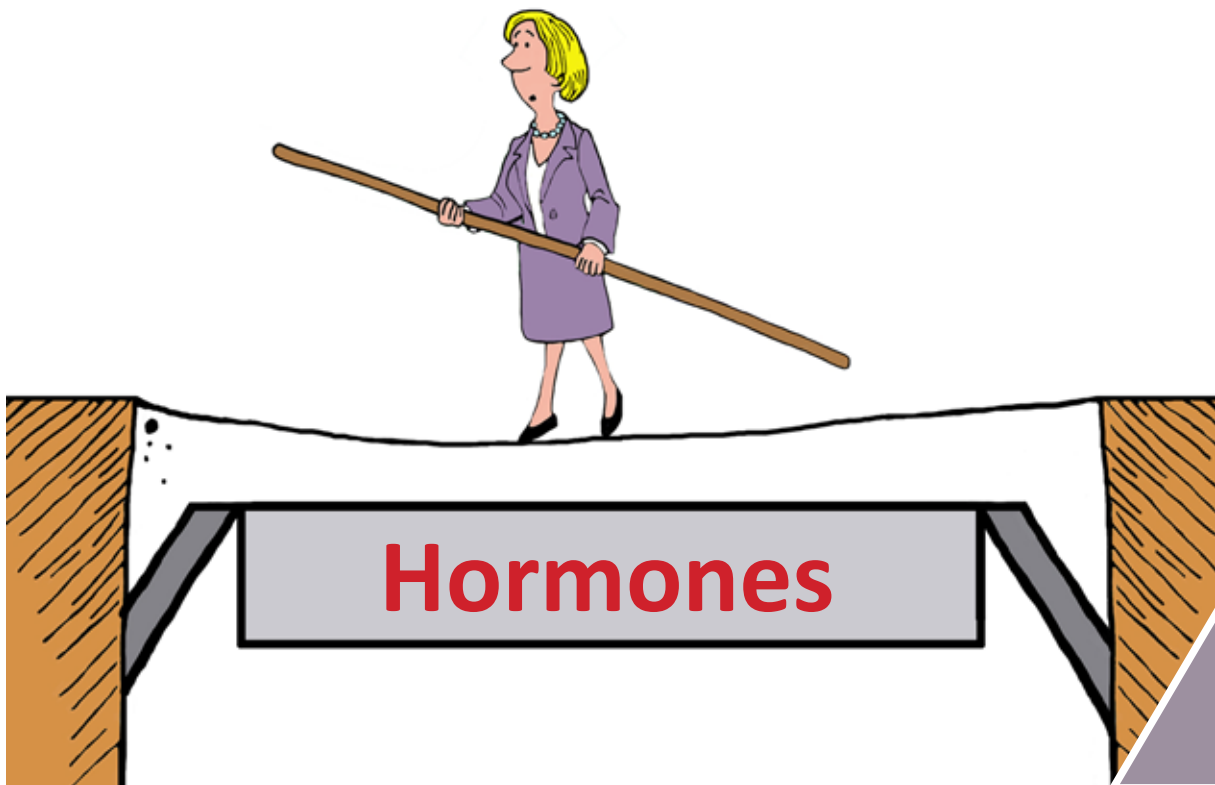




Key Points

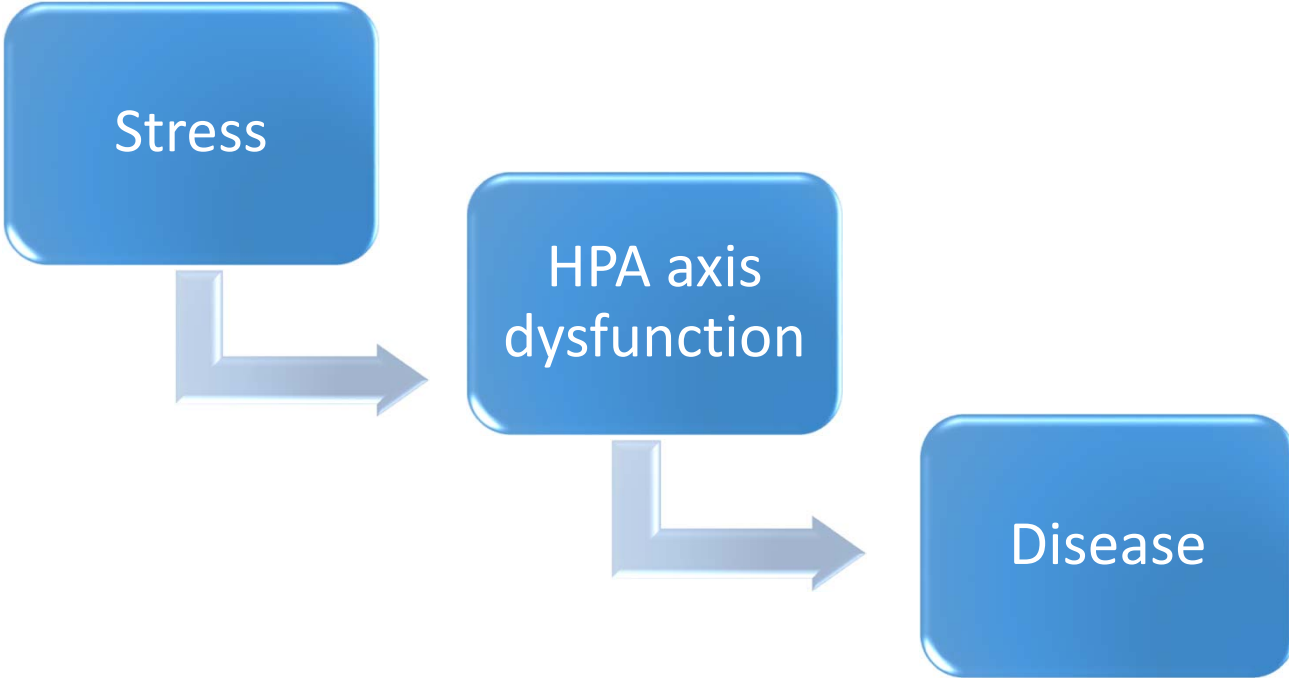
- The typical 28 day cycle is comprised of the follicular and luteal phases
- Changes in the length of the cycle are typically due to a change in the follicular phase
- The cycle should include a follicular and luteal phase spike
- The presence of a follicular spike suggests ovulation, but does not definitively confirm it







Why Evaluate the HPA Axis?

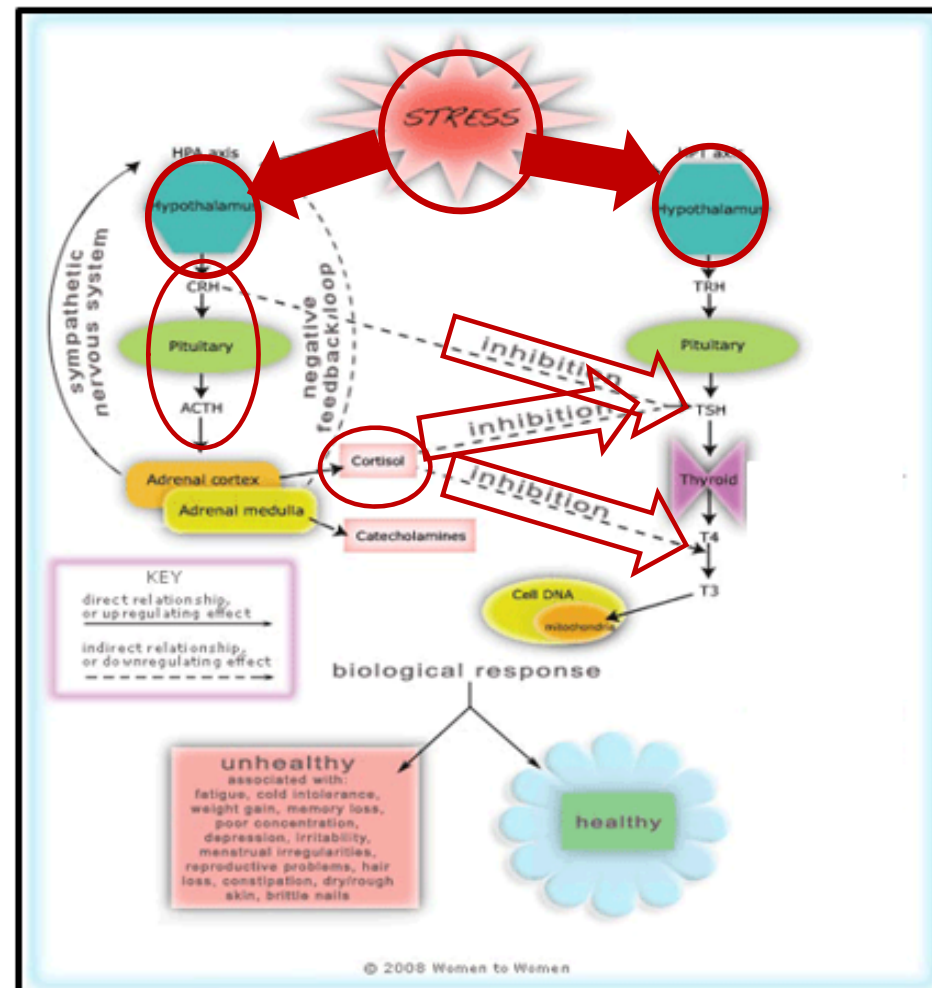


Kern S, et al. *PLoS One*. 2013;8(4):e60647.
Dedovic K, et al. *Neuropsychiatr Dis Treat*. 2015;11:1181-89.
Hamer M, et al. *Eur Heart J*. 2009;31(4):424-29.
Hackett RA, et al. *J Clin Endocrinol Metab*. 2014;99(12):4625-31.
Ennis GE, et al. *Brain Cogn*. 2016;105:66-77.



HPA Axis – HPT Axis Interplay

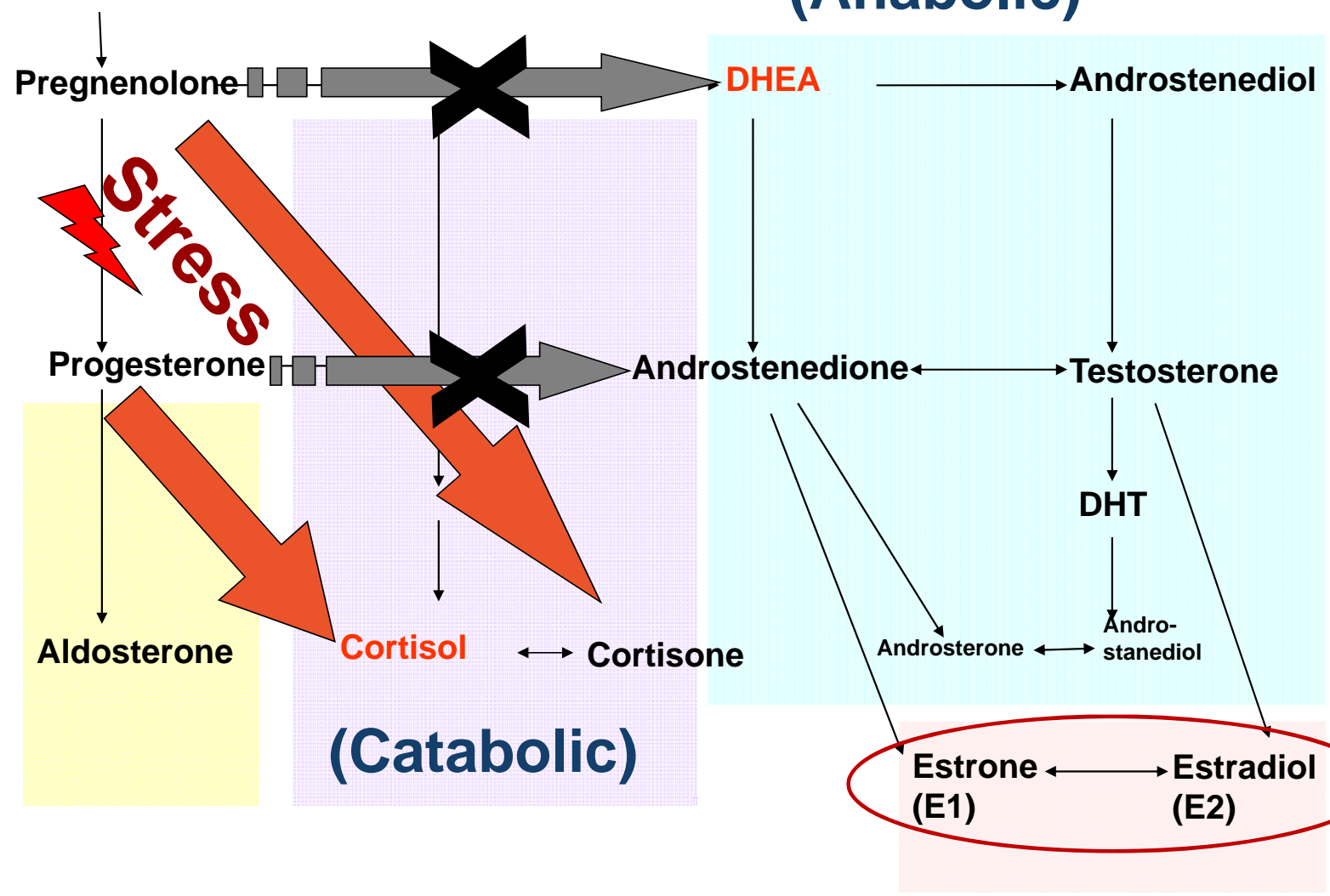
- The HPA axis is a key to a balanced steroidogenic pathway
- Activation of hypothalamus in response to stress AND production of glucocorticoids directly inhibits Thyroid Stimulating Hormone (TSH)
 - May impact thyroid hormone output
- Cortisol inhibits conversion of T4 to T3 which is active at target tissue





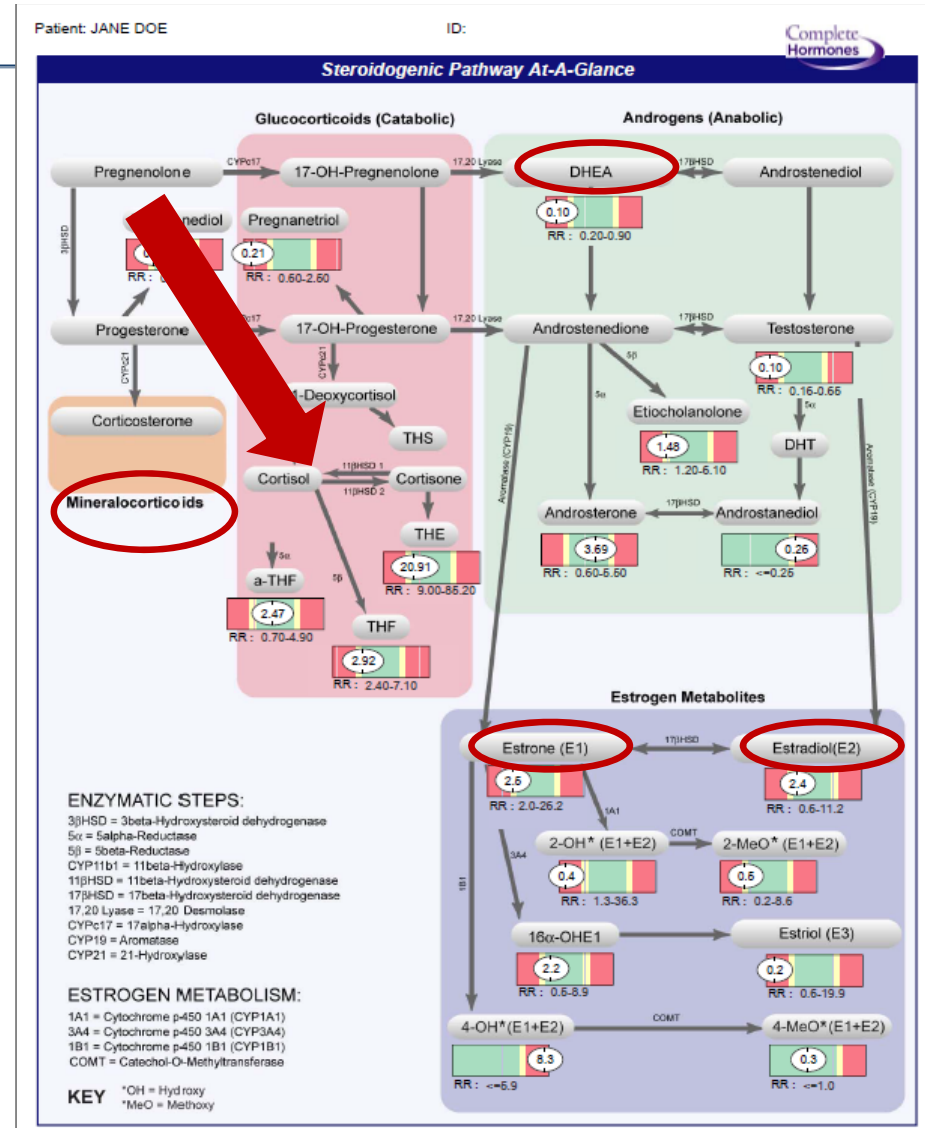
Cholesterol

(Anabolic)



HPA Axis Imbalance

- Stress alters HPA axis balance, increasing cortisol production
 - May impact thyroid and insulin levels
- Stress alters HPA axis, leading to an increase in mineralcorticoids
 - Stimulation of the renin-angiotensin-aldosterone system (RAS) leads to tachycardia and elevated blood pressure





Key Points

- The HPA axis influences hormonal balance
- The HPA axis has an inhibitory effect on the HPT axis, which impacts thyroid hormone production
- Cortisol influences pancreatic, liver, and gut function
- Elevated cortisol influences insulin levels





Conditions Related to Imbalanced Hormones

- Weight gain
- Anxiety
- Fatigue
- Muscle mass loss
- Muscle weakness
- Low libido and sexual performance
- Hair loss
- Sleep disturbances
- Brain fog
- Mood instability
- Hot Flashes
- Vaginal dryness
- Infertility



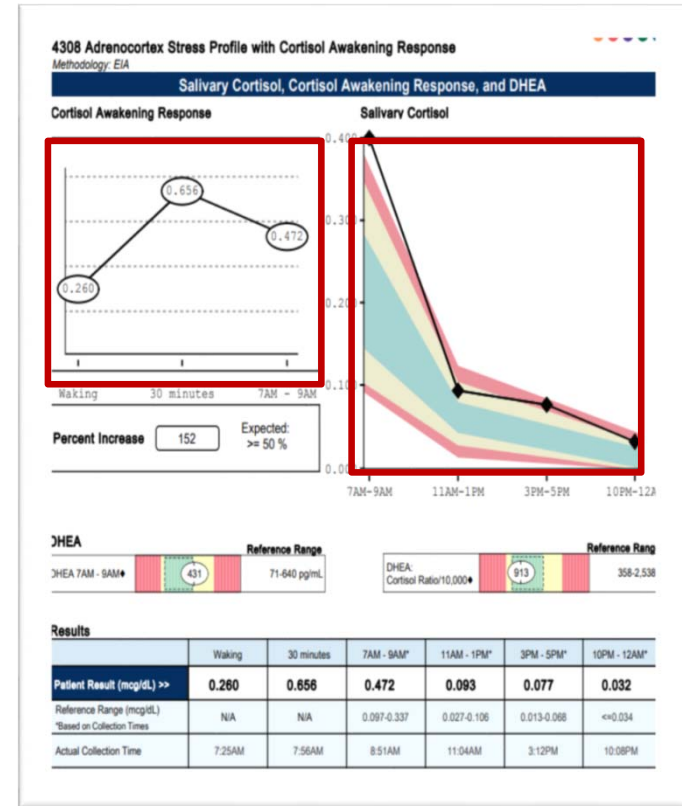
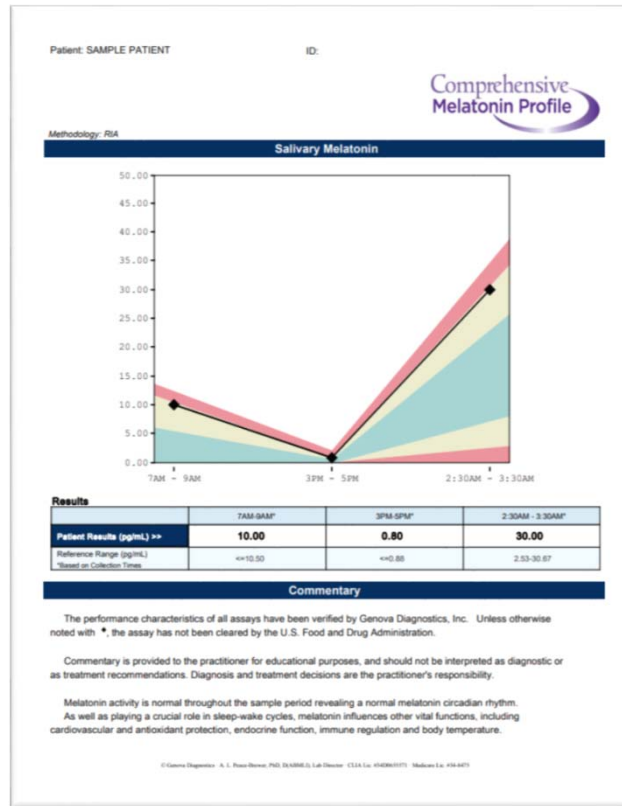
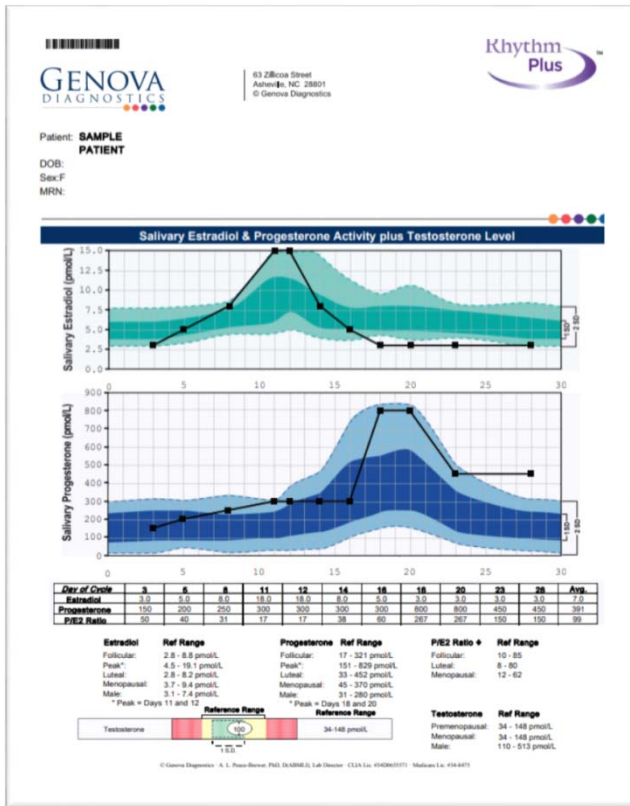
Rhythm™

Rhythm Plus™

- 11 salivary samples spanning 28 day period
 - Estradiol
 - Progesterone
 - Testosterone (1 sample)

- 11 salivary samples spanning 28 day period
 - Estradiol
 - Progesterone
 - Testosterone (1 sample)
- Adrenocortex Stress Profile with or without Cortisol Awakening Response (CAR) -- (4-6 samples)
- Melatonin (3 samples)

Rhythm Plus™





Why the Rhythm *Plus*[™]?

- Salivary hormones provide the best insight into parent hormone levels
- Urinary hormones measure *metabolites* that provide insight into *detoxification* pathways
- The Rhythm profile provides valuable insight into premenopausal patients because it allows a look at the *full cycle*, not just selected moments in time
- Patients should be encouraged to journal how they are feeling during the 4 weeks of collection in order to correlate clinical symptoms with levels of estradiol and progesterone



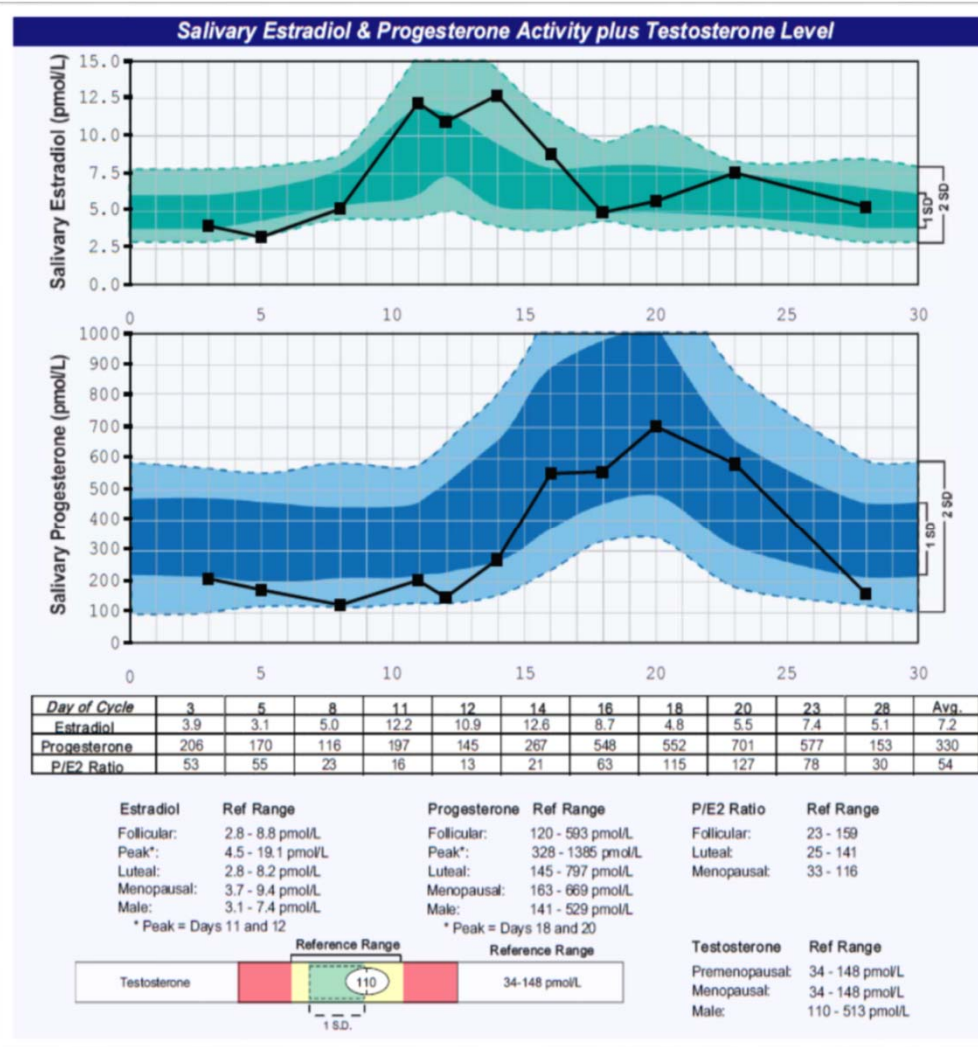


Why the Rhythm *Plus*™?

- The inclusion of the “*Plus*” portion of the test (Adrenocortex Stress Profile and Comprehensive Melatonin Profile) provides data regarding the HPA axis
- Inflammation, toxic exposure, infection, and others can influence the HPA axis
- The HPA axis influences the steroidogenic pathway, including production of estrogens and androgens



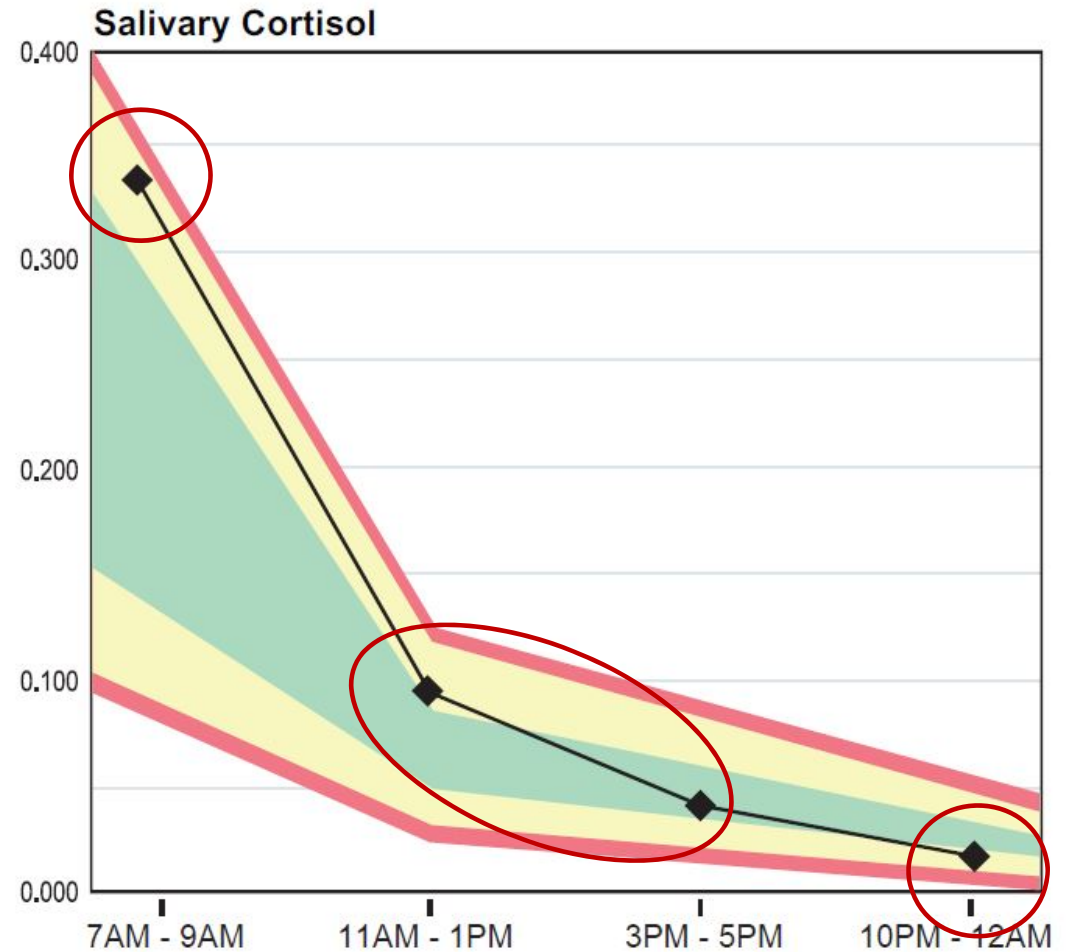
Rhythm™





Rhythm Plus™

- Diurnal Circadian Rhythm
- Cortisol responds to stress which can disrupt the HPA axis
- Elevated cortisol increases insulin resistance and glycemic dysregulation
- Elevated cortisol influences the circadian rhythm of hormones
- Cortisol secretion increases in response to inflammation
- The HPA axis influences the production of DHEA, testosterone, and estrogen



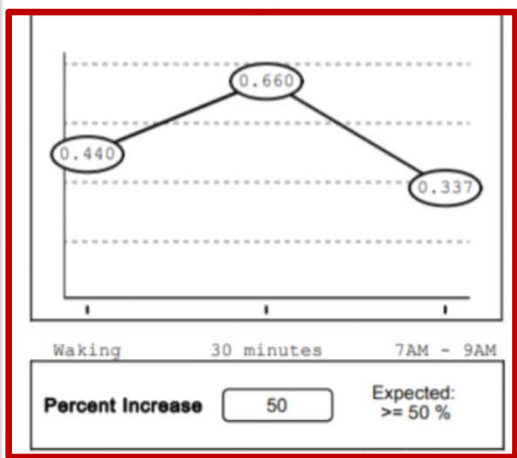


Adrenocortex Stress Profile WITH CORTISOL AWAKENING RESPONSE

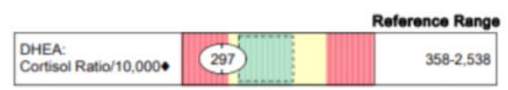
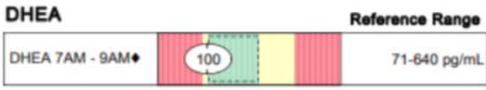
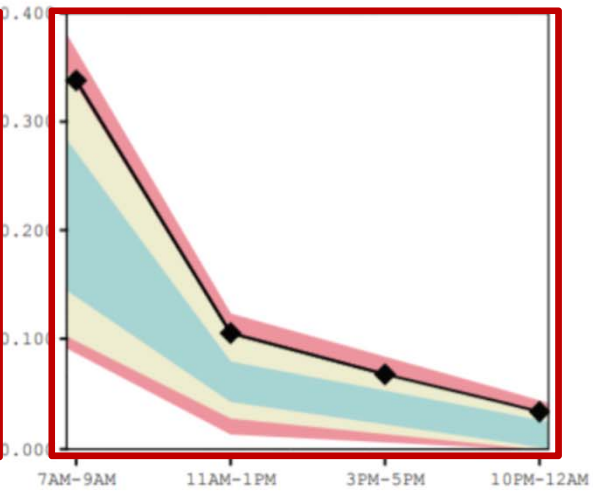
Methodology: EIA

Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response



Salivary Cortisol



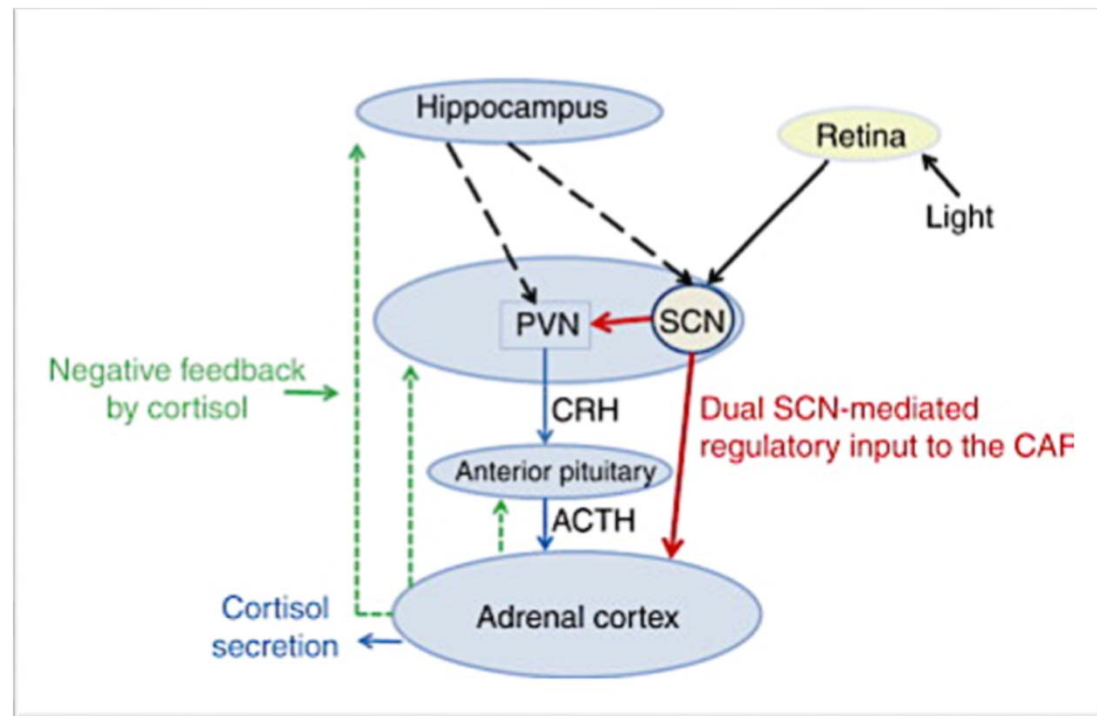
Results

	Waking	30 Minutes	7AM-9AM*	11AM-1PM*	3PM-5PM*	10PM-12AM*
Patient Result (mcg/dL) >>	0.440	0.660	0.337	0.106	0.068	0.034
Reference Range (mcg/dL) <small>*Based on Collection Times</small>	N/A	N/A	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
Actual Collection Time	7:05AM	7:35AM	8:00AM	11:00AM	3:00PM	11:00PM

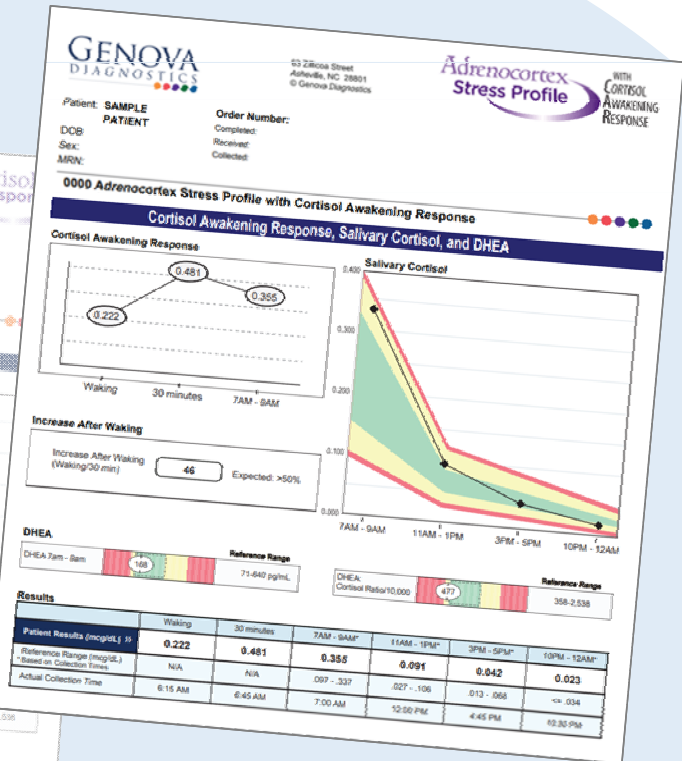


Cortisol Awakening Response (CAR)

- Transient increase upon awakening
- Distinct physiologic mechanism
- Unrelated to diurnal rhythm
- HPA axis resiliency
- Ability to cope with anticipated stressors



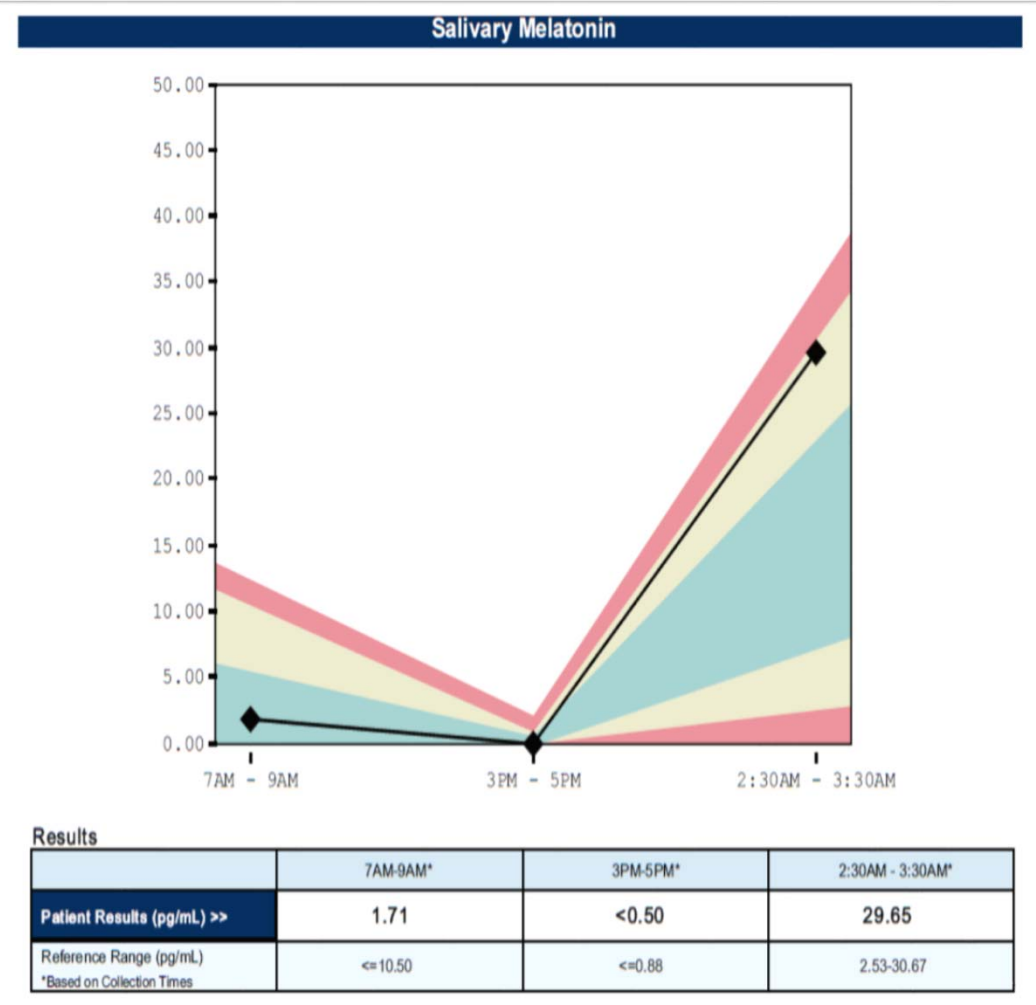
Cortisol Testing Options



Rhythm Plus™ Comprehensive Melatonin Profile

Melatonin:

- Impacts the release of sex hormones
- Decreases levels of cortisol
- Is a strong antioxidant
- Influences mood and sleep
- Works as an anti-inflammatory





Case Study #1

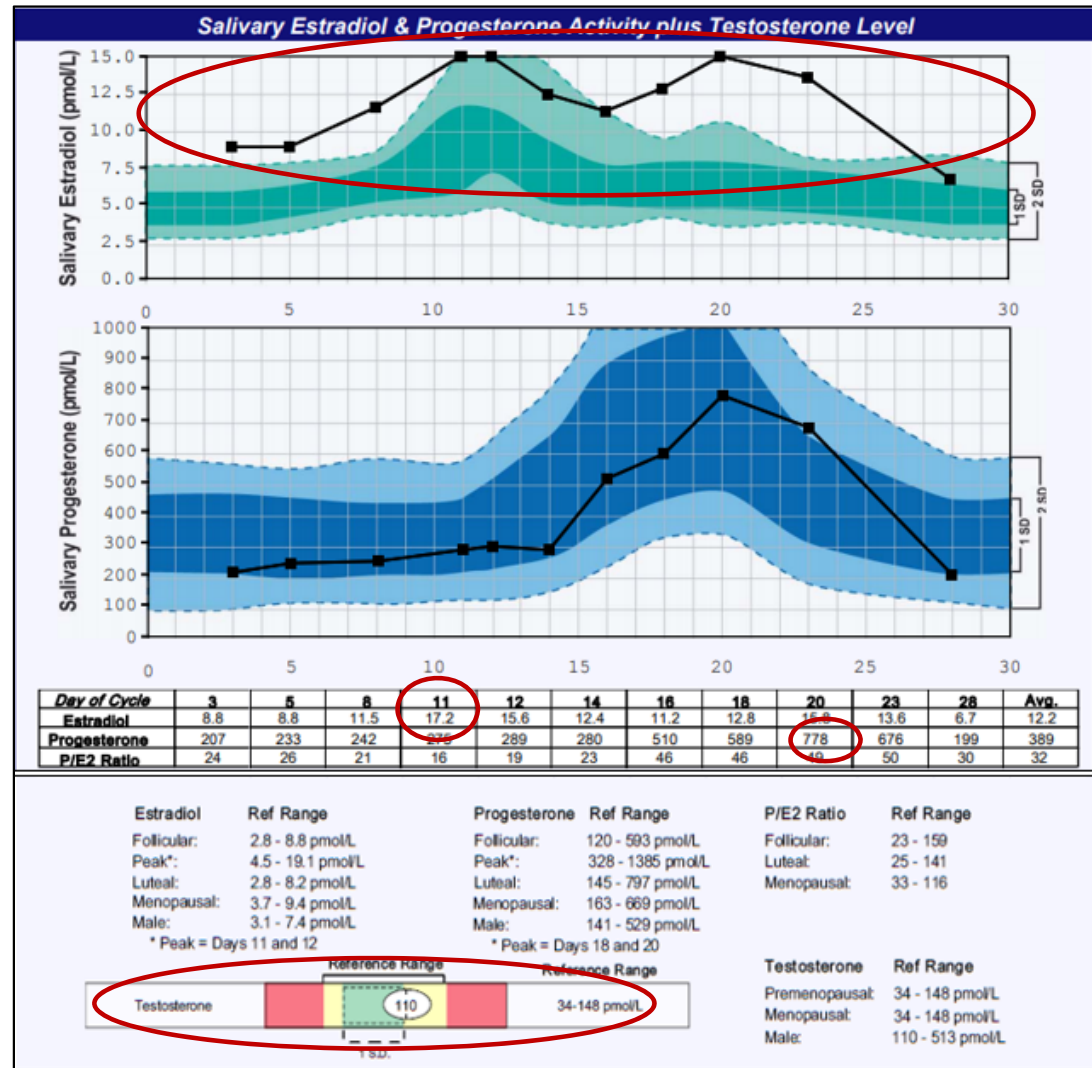
22 y/o female

- Menstrual cycles
 - Menarche age 13
 - Cycles reported as regular
 - Weight gain around the waist
 - Breast tenderness
 - Sleep disturbances
- Thyroid WNL
- Iron is WNL
- Fasting glucose 109, HbA1c 5.8, fasting insulin 12
- Lifestyle
 - Nursing student
 - Standard American Diet
 - Sedentary



Case Study #1 Rhythm

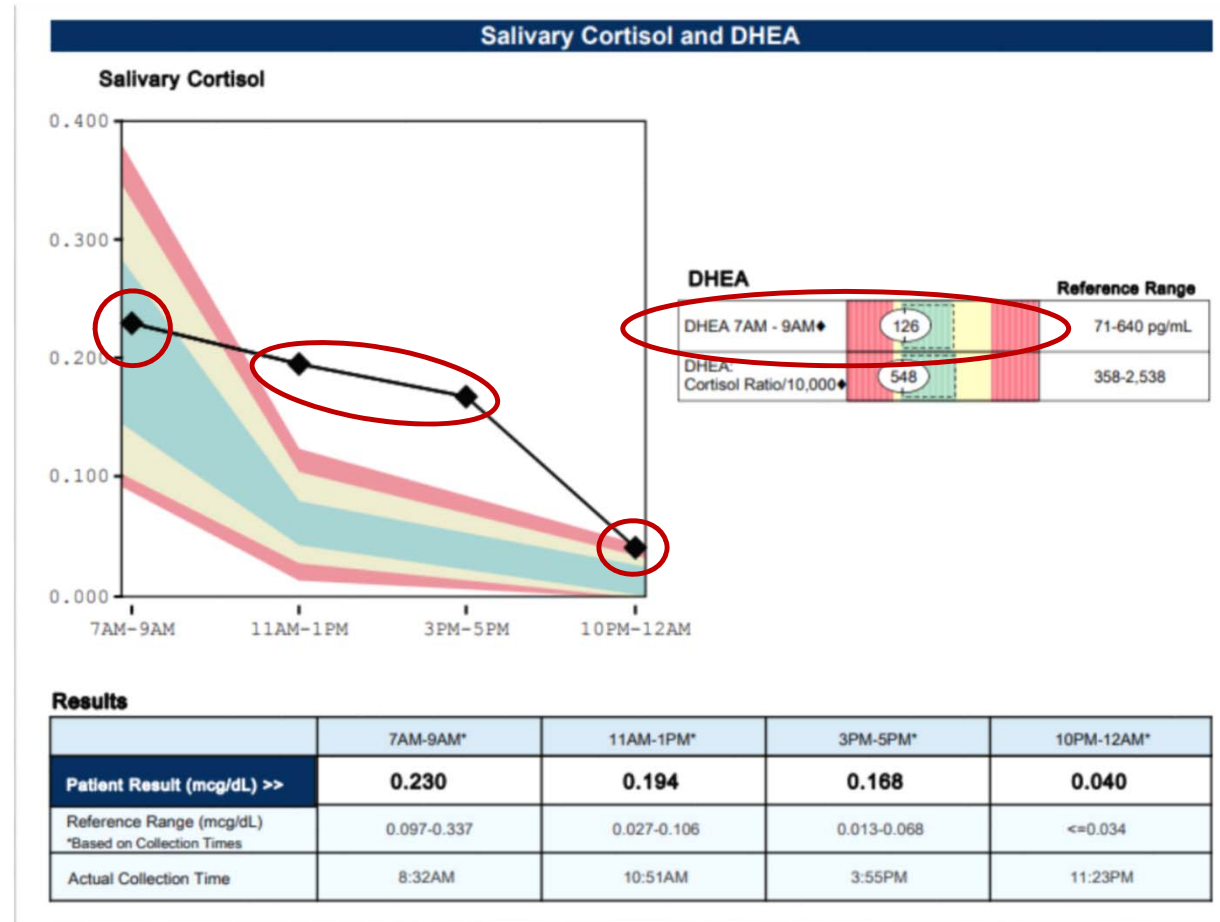
- Elevated estradiol with follicular spike on day 11
- Luteal phase peak for progesterone on day 20
- Testosterone within normal range
- Overall imbalance suggests estrogen dominance





Adrenocortex Stress Profile

- Waking cortisol level normal
- Two afternoon cortisol findings elevated, may reflect stresses specific to that day, also indicative of a strong stress response
- Evening cortisol elevated, consistent with sleep issues and the need to address adrenal balance
- DHEA in the lower portion of the reference range, but only one moment in time, can be variable
- High cortisol associated with abdominal weight-gain

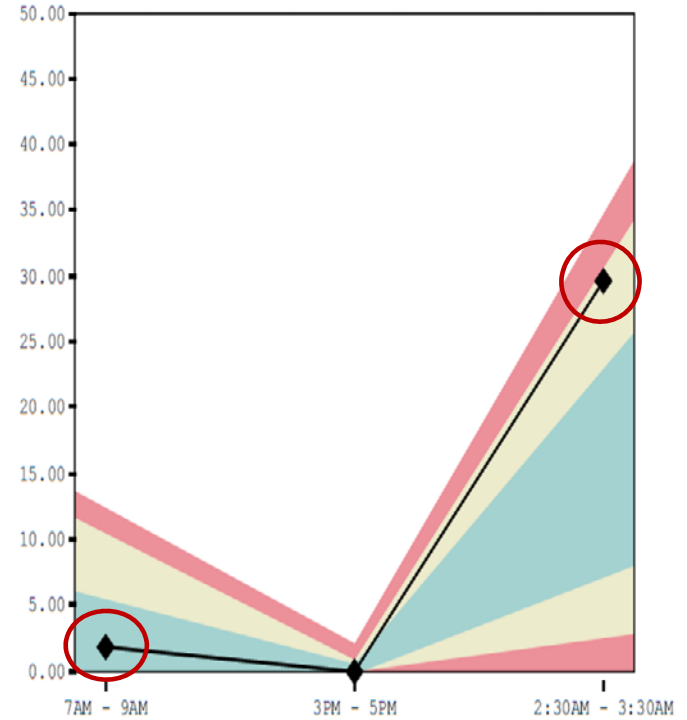




Case Study #1: Melatonin

- Waking melatonin well within normal range
- Night level is high/normal -- this can be an adaptive response to the elevated evening cortisol level

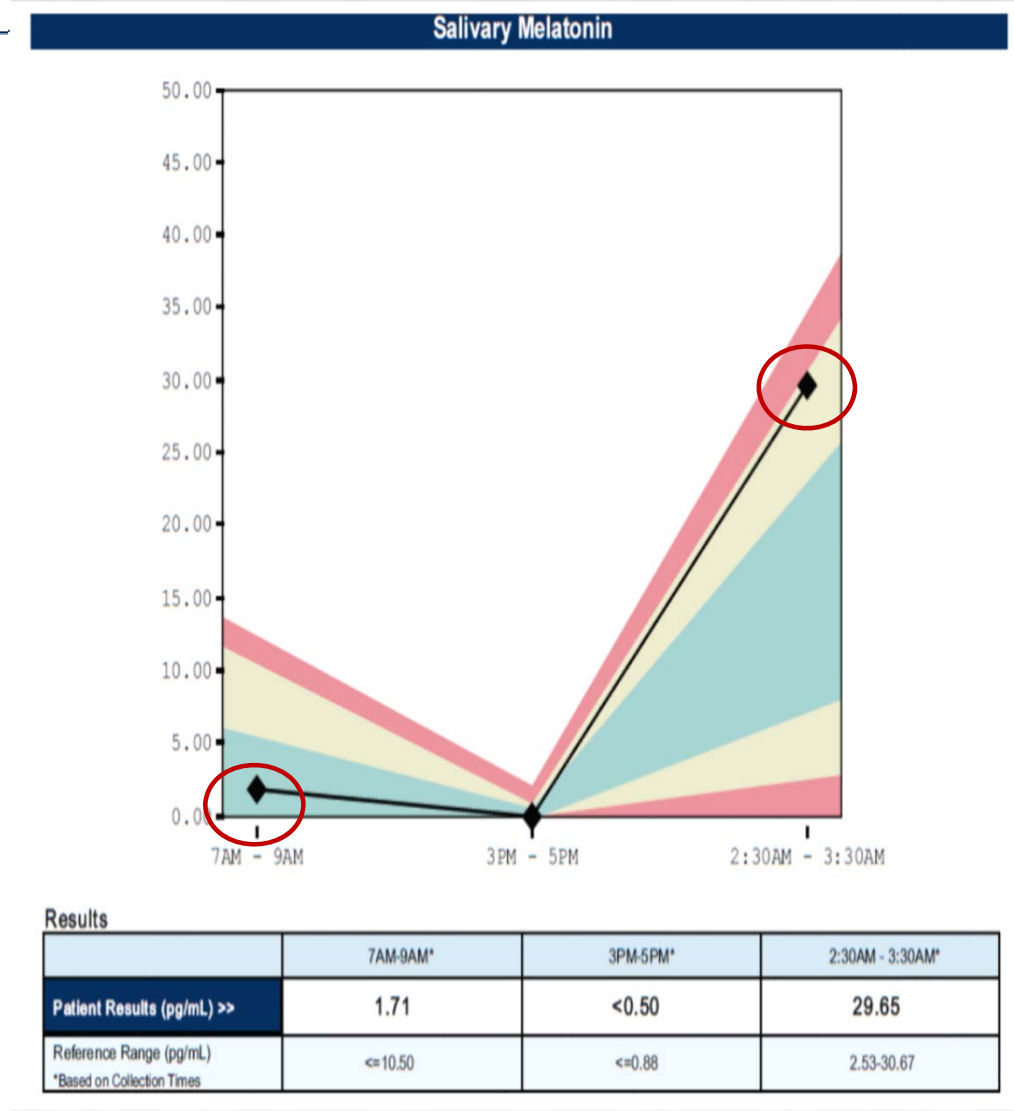
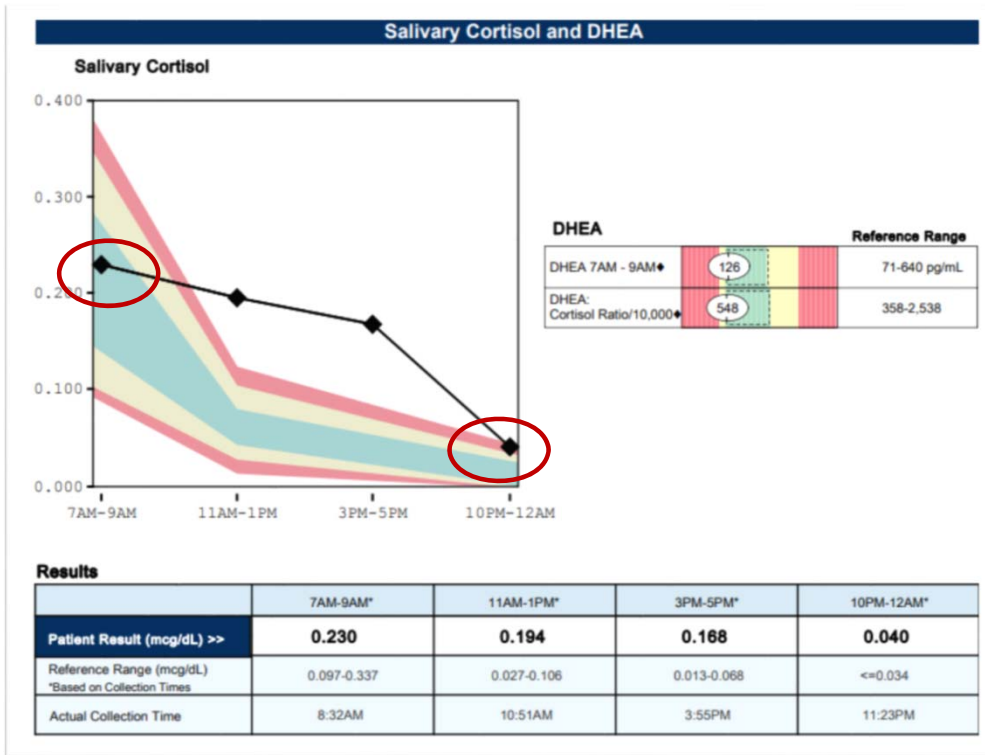
Salivary Melatonin



Results

	7AM-9AM*	3PM-5PM*	2:30AM - 3:30AM*
Patient Results (pg/mL) >>	1.71	<0.50	29.65
Reference Range (pg/mL)	<= 10.50	<= 0.88	2.53-30.67
<small>*Based on Collection Times</small>			

Case Study #1





Case Study #1: Treatment Options

- Elevated Estrogen
 - Support estrogen detoxification: Cruciferous vegetables, consider DIM
 - Calcium D-Glucarate
- Adrenal support
 - Relora for adrenal support
 - Nutrition: multivitamin, eat fatty fish such as salmon 3x week
 - **Mediterranean diet** would provide these needed nutrients
 - Increase: cruciferous vegetables, antioxidant rich foods, low-mercury fish, and water
 - Decrease: processed foods
- General
 - Consider **HeartMath** for stress reduction
 - Magnesium and phosphatidylserine to improve sleep





Case Study #2

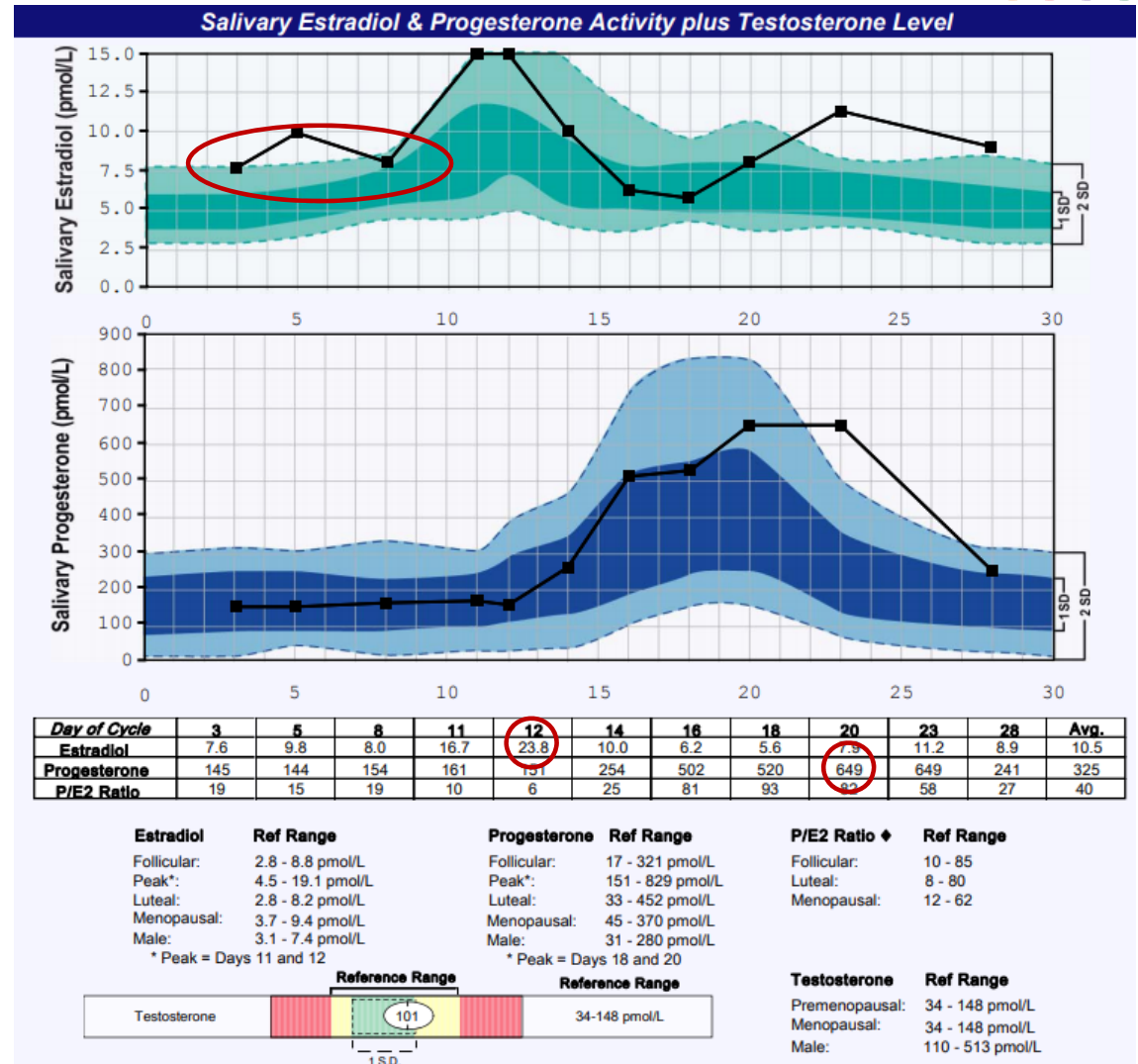
36 y/o female

- Menstrual cycle
 - Cycles every 28 days
 - Dysmenorrhea
 - 7 y/o child
- Labs and Physical Exam
 - Standard labs and thyroid WNL
 - BMI WNL
- GI: constipation and abdominal discomfort
- Diet: Paleo
- Lifestyle
 - Weekend warrior
 - Biking, running, and rowing
 - 5-7 hours of sleep per night
 - Stressful occupation



Case Study #2

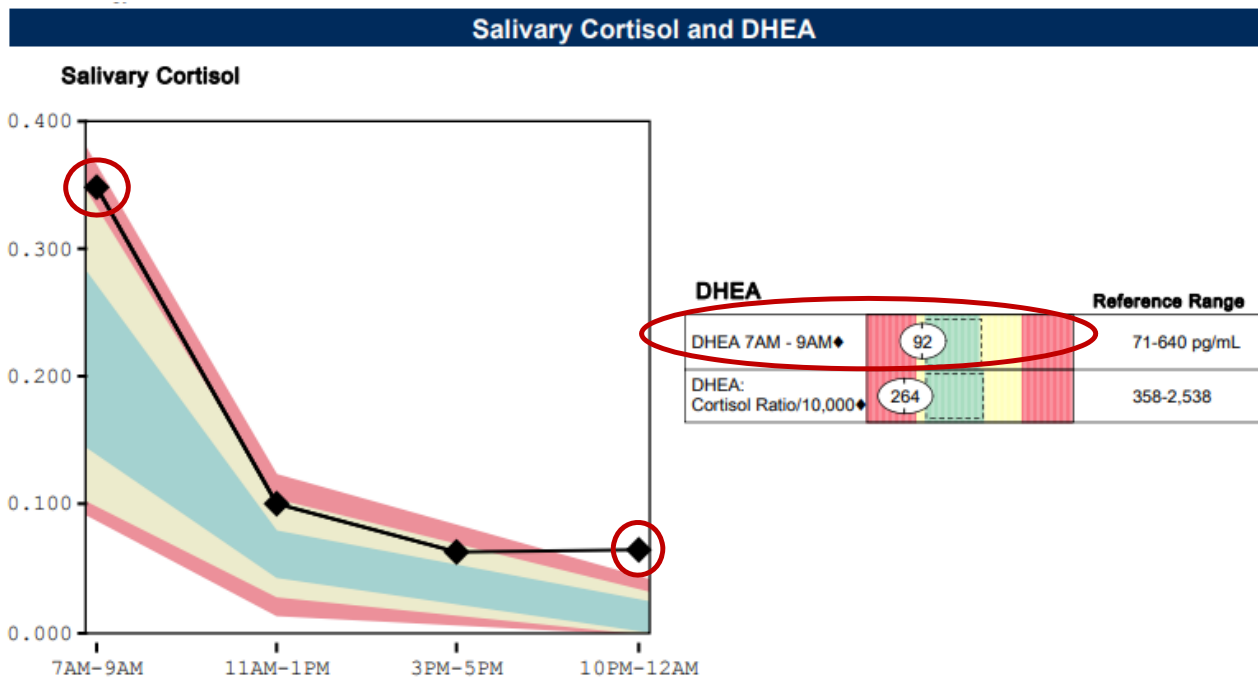
- Luteal phase peak at day 20
- Follicular phase spike at day 12
- Consider estrogen dominance during the follicular phase of the cycle
- Testosterone within the reference range





Case Study #2: ASP

- High waking cortisol
- High evening cortisol, sleep issues likely
- Low DHEA with a high level of physical exercise



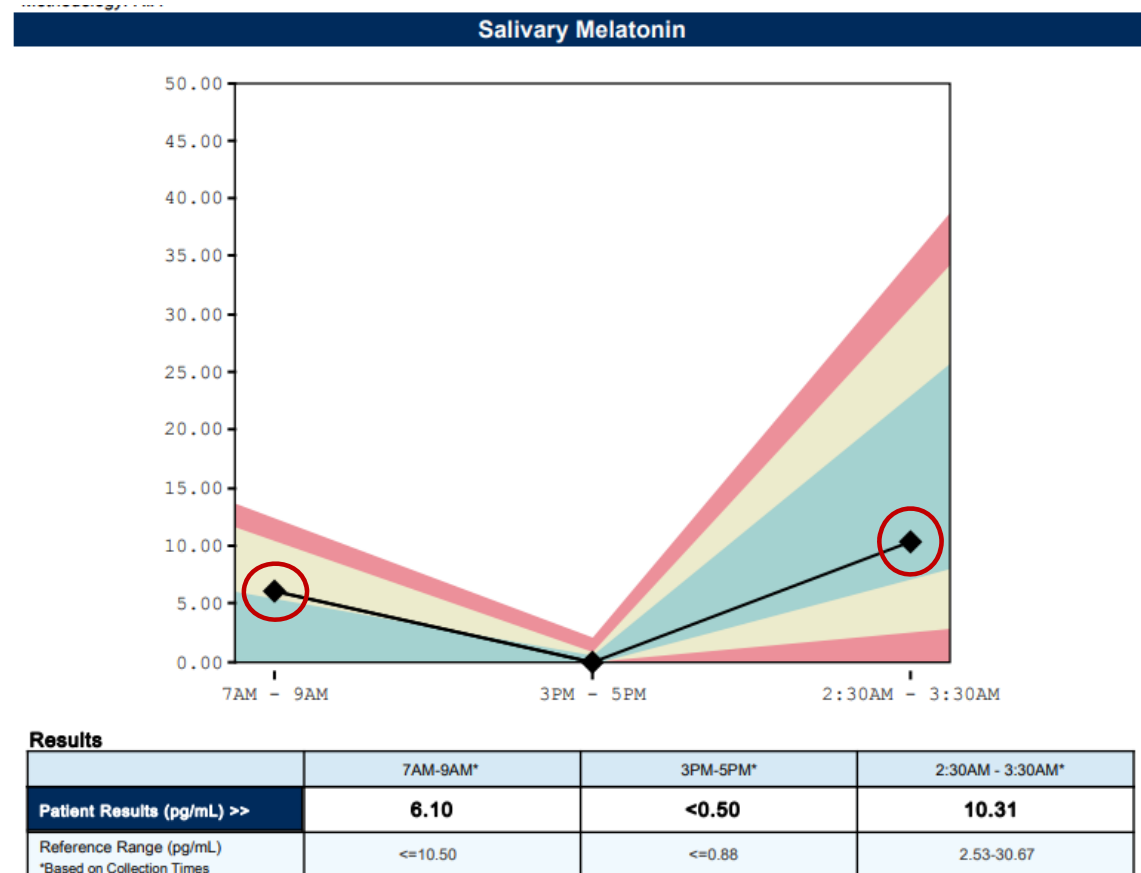
Results

	7AM-9AM*	11AM-1PM*	3PM-5PM*	10PM-12AM*
Patient Result (mcg/dL) >>	0.348	0.100	0.063	0.065
Reference Range (mcg/dL)	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
<small>*Based on Collection Times</small>				



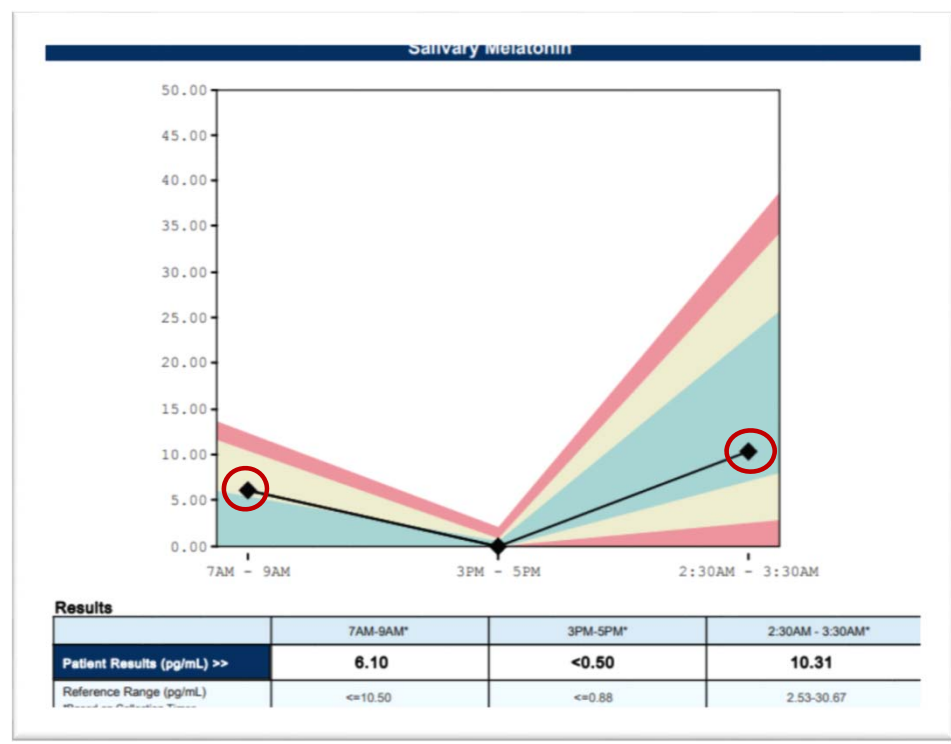
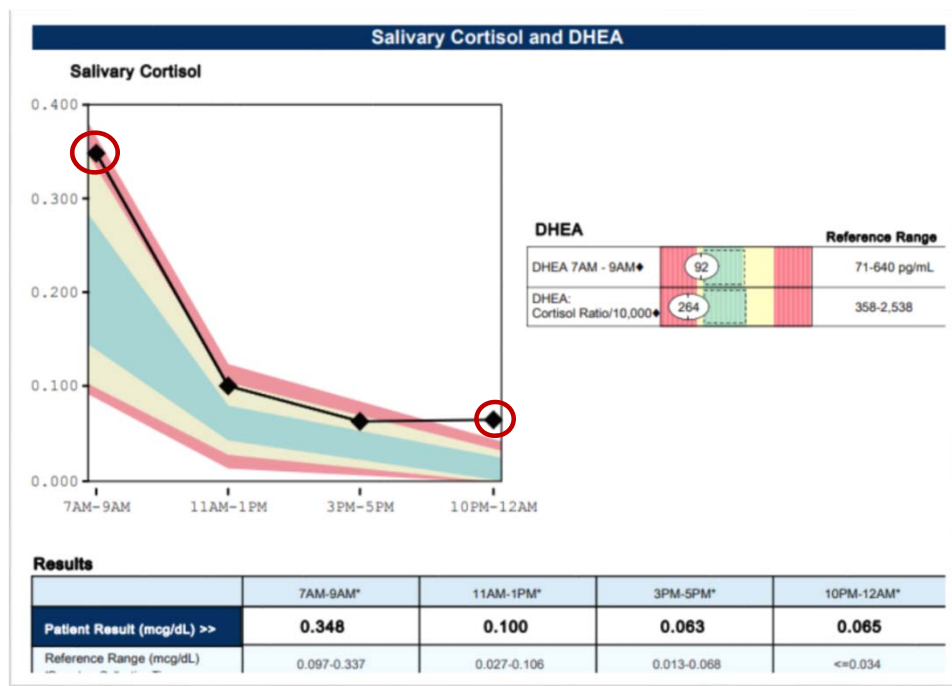
Case Study #2: Melatonin

- Although the 7-AM melatonin is in the reference range, it is in the higher end of the range
- Paired with an elevated morning cortisol, this may be interpreted as an appropriate level of morning melatonin
- A high evening cortisol can lead to an adaptive change in the night-time melatonin over time
- High cortisol with lower melatonin means this patient will likely wake up tired
- It is essential that the patient does not collect the melatonin in the presence of light, which will lower the level





Case Study #2





Case Study #2 Treatment

- Adrenal support
 - Relora, Rhodiola
 - Multivitamin
- Sleep
 - Magnesium at night
 - L-Theanine to reset the HPA axis at night
 - Phosphatidylserine 3 hours before bed
- General
 - **HeartMath**
 - Change from high protein to **Mediterranean diet**
 - **GI Effects Comprehensive, SIBO test**, probiotics to balance gut, and support detoxification
 - Emphasis on helping her *get more sleep*





Case Study #3

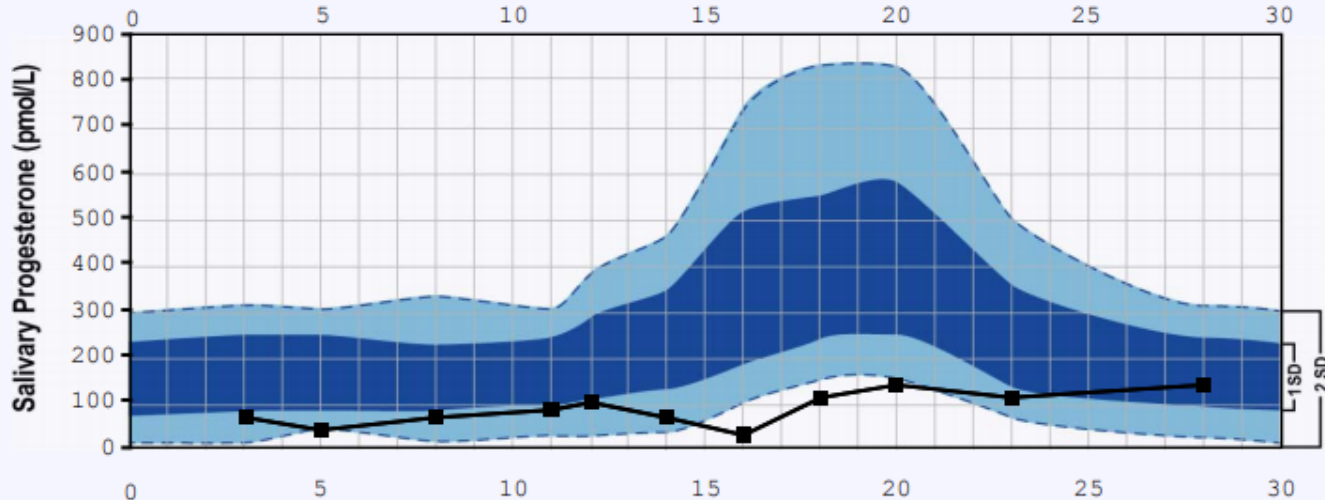
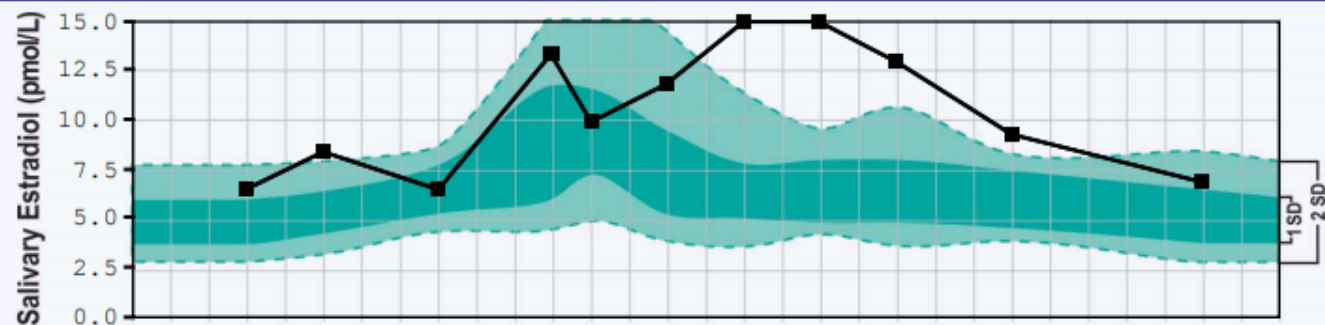
34 y/o female

- Menstrual cycle 28 days
 - Difficulty maintaining pregnancy
- Labs and Physical Exam
 - Labs indicate low thyroid, no medication
 - BMI WNL
 - GI chronic constipation
- Lifestyle
 - Stressful job
 - Anxious and irritable
 - Insufficient sleep





Salivary Estradiol & Progesterone Activity plus Testosterone Level

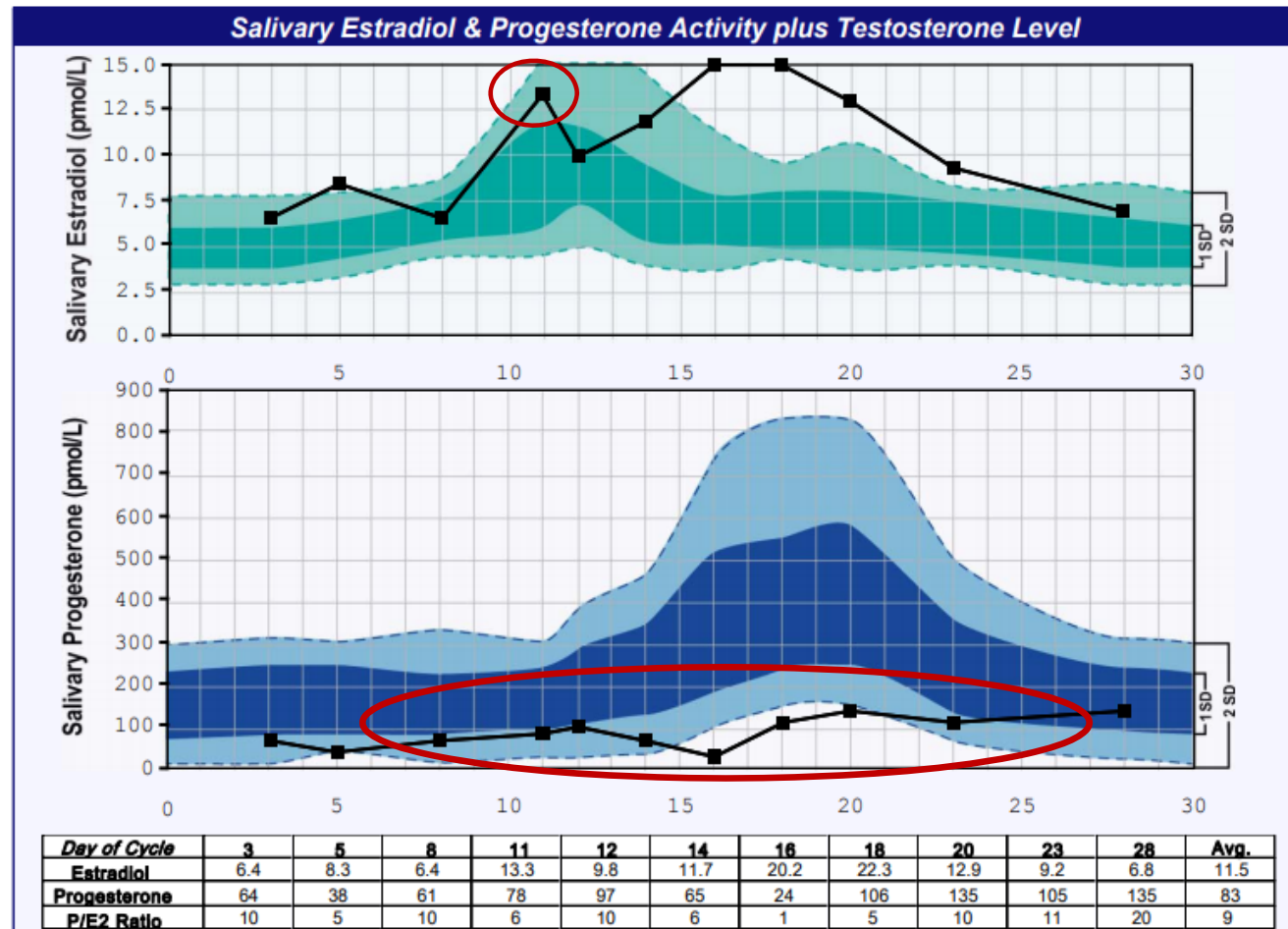


Day of Cycle	3	5	8	11	12	14	16	18	20	23	28	Avg.
Estradiol	6.4	8.3	6.4	13.3	9.8	11.7	20.2	22.3	12.9	9.2	6.8	11.5
Progesterone	64	38	61	78	97	65	24	106	135	105	135	83
P/E2 Ratio	10	5	10	6	10	6	1	5	10	11	20	9



Case Study #3

- Low progesterone throughout her cycle
- No luteal phase elevation detected
- Follicular spike at day 11
- Without a luteal increase at around day 18, the uterine lining is not prepared for implantation
- Estradiol is robust, consider estrogen dominance

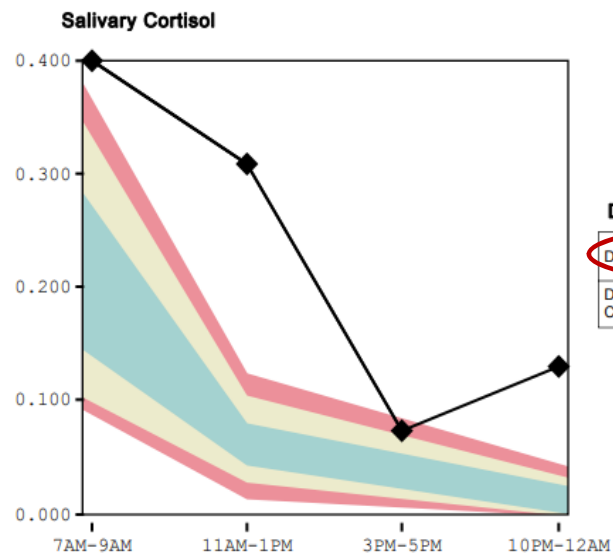




Case Study #3

- Elevated cortisol corresponds with her sleep issues
- Low DHEA paired with elevated cortisol and hypothyroid reflect HPA imbalance; consider DHEA support due to her low measured level
- Elevated cortisol is associated with reduced T3, T4 production, continue monitoring her thyroid while supporting adrenal balance
- Consider one year of nutraceutical treatment to correct HPA axis; once balanced, stop nutraceuticals before providing progesterone to promote pregnancy

Salivary Cortisol and DHEA



DHEA	Reference Range
DHEA 7AM - 9AM \blacklozenge 57	71-640 pg/mL
DHEA: Cortisol Ratio/10,000 \blacklozenge 128	358-2,538

Results

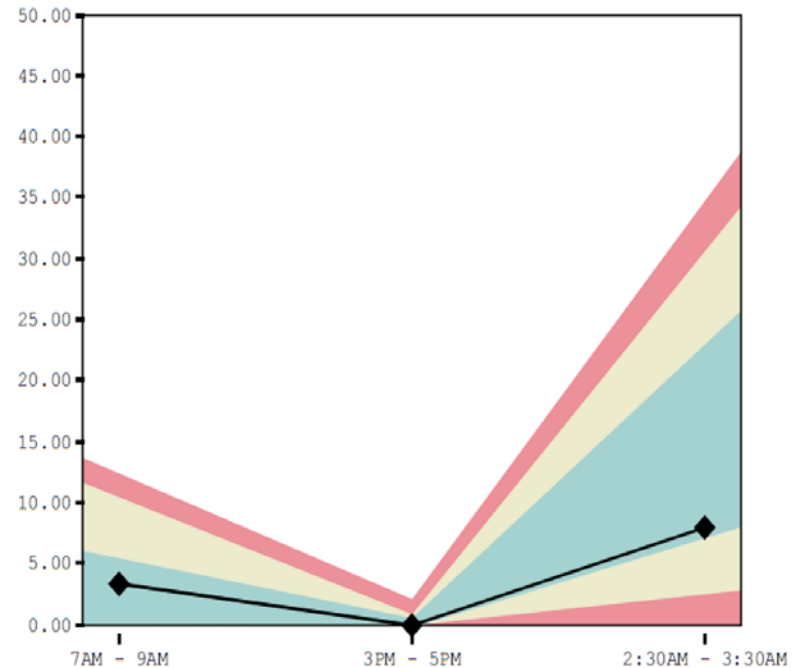
	7AM-9AM*	11AM-1PM*	3PM-5PM*	10PM-12AM*
Patient Result (mcg/dL) >>	0.444	0.308	0.073	0.130
Reference Range (mcg/dL) *Based on Collection Times	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
Actual Collection Time	7:39AM	11:56AM	4:26PM	10:12PM



Case Study #3

- Morning melatonin appears well within the normal range
- Evening levels are on the lower end of normal and may be a response to the elevated evening cortisol or an exposure to light while collecting the sample
- Elevation of evening melatonin may be an adaptive effort to suppress high evening cortisol

Salivary Melatonin

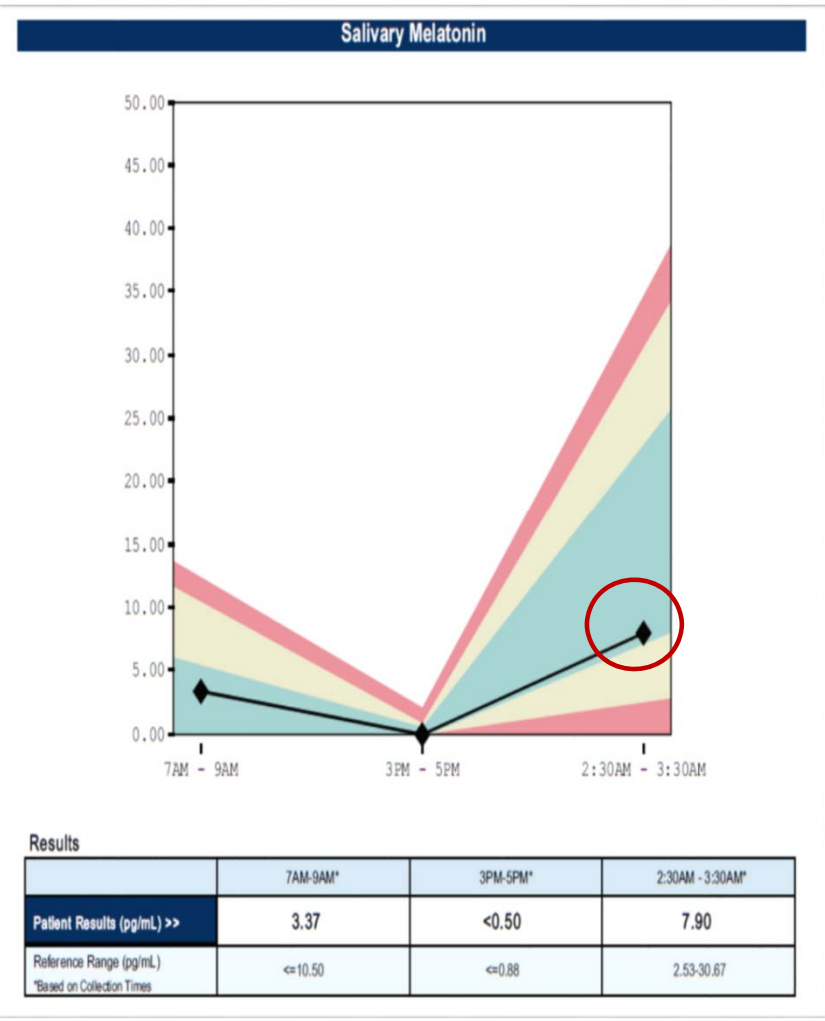
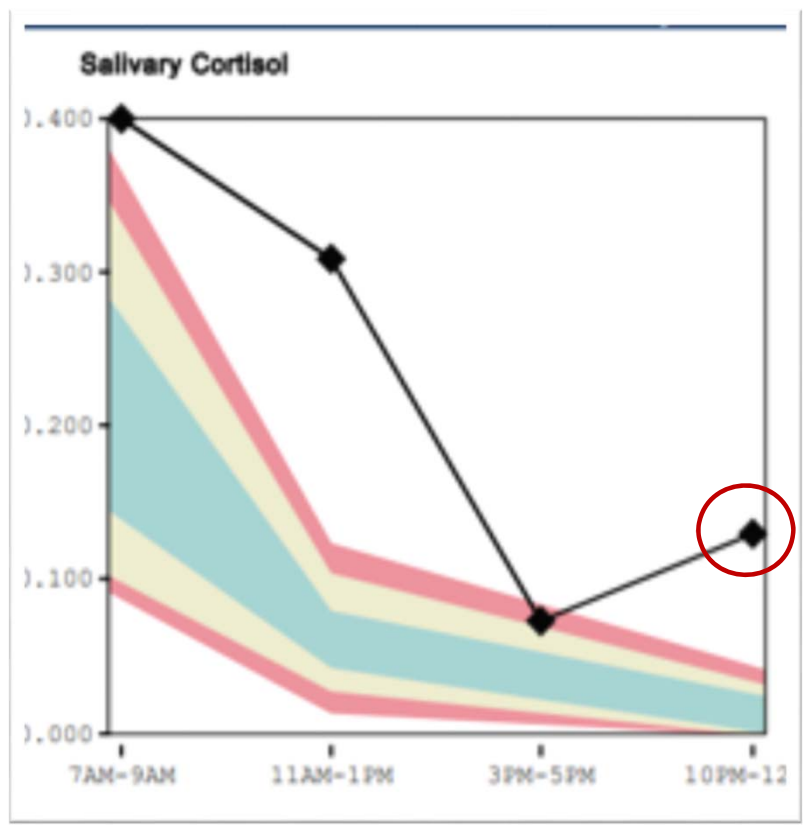


Results

	7AM-9AM*	3PM-5PM*	2:30AM - 3:30AM*
Patient Results (pg/mL) >>	3.37	<0.50	7.90
Reference Range (pg/mL)	<=10.50	<=0.88	2.53-30.67
<small>*Based on Collection Times</small>			



Case Study #3



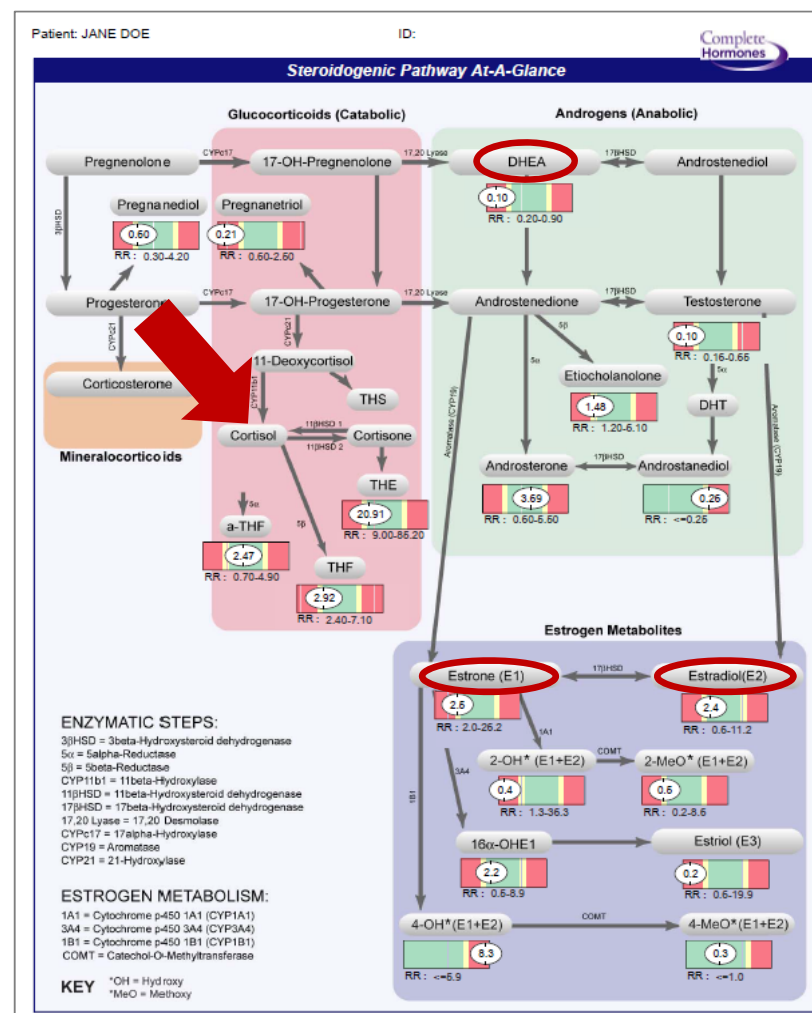
Results

	7AM-9AM*	3PM-5PM*	2:30AM-3:30AM*
Patient Results (pg/mL) >>	3.37	<0.50	7.90
Reference Range (pg/mL)	<=10.50	<=0.88	2.53-30.67
<small>*Based on Collection Times</small>			



Address the HPA Axis Imbalance

- With HPA imbalance indicated on ASP, the patient can be expected to convert progesterone into higher levels of cortisol
- Providing thyroid medication is less likely to be effective; high cortisol production leads to less availability of T3 and T4
- One can provide DHEA while working to balance adrenal function since her levels are so low
- Consider treating the HPA axis for one year with nutraceuticals before supplementing progesterone to address a potential pregnancy
- One can provide progesterone to address symptoms of estrogen dominance, but progesterone to support a pregnancy should come after HPA axis balance is achieved
- Once balanced, stop nutraceuticals before prescribing progesterone to support a pregnancy





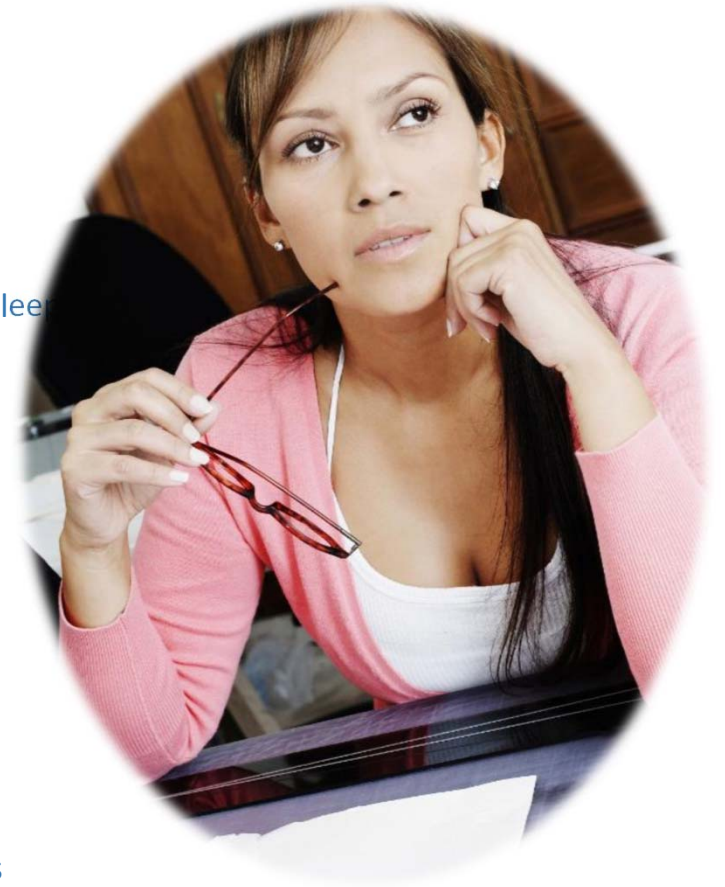
Case Study #3: Treatment

- **HPA Axis Support**

- DHEA supplementation while balancing adrenal/cortisol levels
- Relora
- L- Theanine, magnesium, epsom salt baths for relaxation, needs down time, sleep
– phosphatidylserine 3 hours before bed
- Fix her HPA axis while monitoring her thyroid

- **General**

- **Mediterranean diet:**
 - Increase: cruciferous vegetables, antioxidant rich foods, nuts and seeds
 - Elimination diet for dairy and gluten
 - Digestive: supporting elimination to support detoxification
- **GI Effects Comprehensive**, SIBO test
- Probiotics
- Multivitamin
- **Complete Hormones:** estrogen metabolite testing, determine how well she is detoxifying her estrogen





Summary of Key Points

- The typical 28 day cycle is comprised of the follicular and luteal phases
- Changes in the length of the cycle are typically due to a change in the follicular phase
- The cycle should include a follicular and luteal phase spike
- The presence of a follicular spike suggests ovulation, but does not definitively confirm it
- The HPA axis influences hormonal balance
- The HPA axis has an inhibitory effect on the HPT axis, which impacts thyroid hormone production
- Cortisol influences pancreatic, liver, and gut function
- Elevated cortisol influences insulin levels





Stephen Goldman, DC
Presenter



Explore

WWW.GDX.NET

*for more information and
educational resources, including...*

LEARN GDX – Brief video modules

LIVE GDX – Previous webinar recordings

GI University – Focused learning modules

Conferences – Schedule of events we attend

Test Menu – Detailed test profile information

MY GDX – Order materials and get results

Questions?



Additional Questions?

US Client Services: 800-522-4762

UK Client Services: 020.8336.7750

Please schedule a complimentary appointment with one of our Medical Education Specialists for questions related to:

- Diagnostic profiles featured in this webinar
- How Genova's profiles might support patients in your clinical practice
- Review a profile that has already been completed on one of your patients

We look forward to hearing from you!



Upcoming ^{LIVE} GDX Webinar Topics

- January 23, 2019 - Case Study Review: SIBO and GI Effects
 - Doctor Jill Carnahan
- February 27, 2019 – Menopause, Insulin Resistance, and Alzheimer’s: What is the Link?
 - Doctor Filomena Trindade
- March 27, 2019 – Male Hormones: What You Need to Know
 - Pam Smith
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Utilizing the Rhythm Plus™ Profile

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