Endo+

A New Approach to Metabolic Medicine Testing

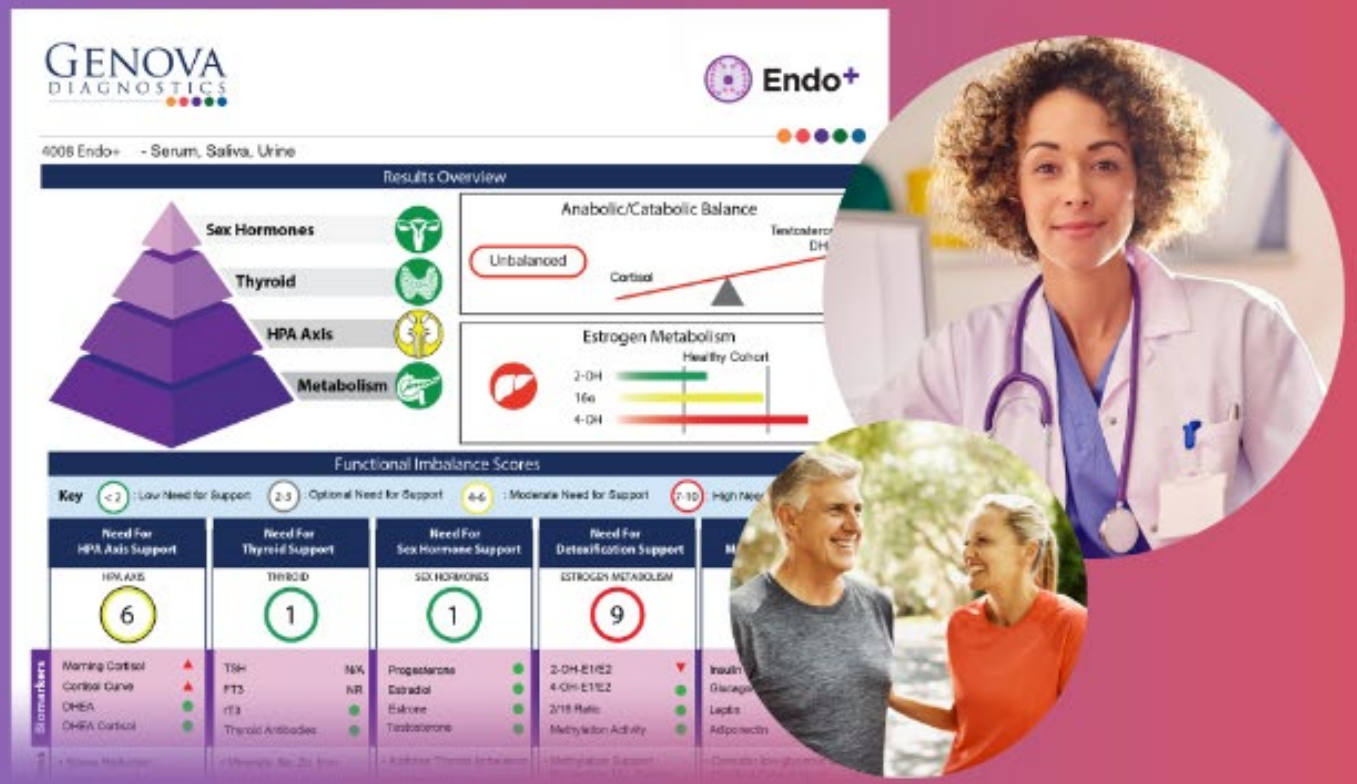
Pamela W. Smith, M.D., MPH, MS

GENOVA DIAGNOSTICS®

Objectives for This Presentation

- Understand the role sex hormones play in the body
- Review the physiology of thyroid hormone function
- Examine estrogen metabolism in the body
- Review the function of melatonin
- Explore genetics

GENOVA DIAGNOSTICS



Endo+

Endo+ — The Most Comprehensive Hormone Evaluation Available

SPECIMEN TYPE: SERUM/SALIVA/URINE

TURNAROUND TIME: 7 - 21 DAYS

Only healthcare providers licensed in their state may order laboratory testing.

Turnaround times are estimates. Detailed order tracking is available in myGDX.

Find a Doctor

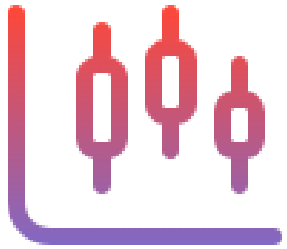
Provider Login / Order

GENOVA DIAGNOSTICS

Unravel the Mysteries of Hormonal Health with Endo+

Endo+ sets the standard for comprehensive hormone evaluations, assessing thyroid, adrenal, melatonin, and sex hormones, along with estrogen metabolism.

Tailor hormonal testing to each patient's needs with a customizable approach that ensures patients receive exactly what's needed for their unique health situation.

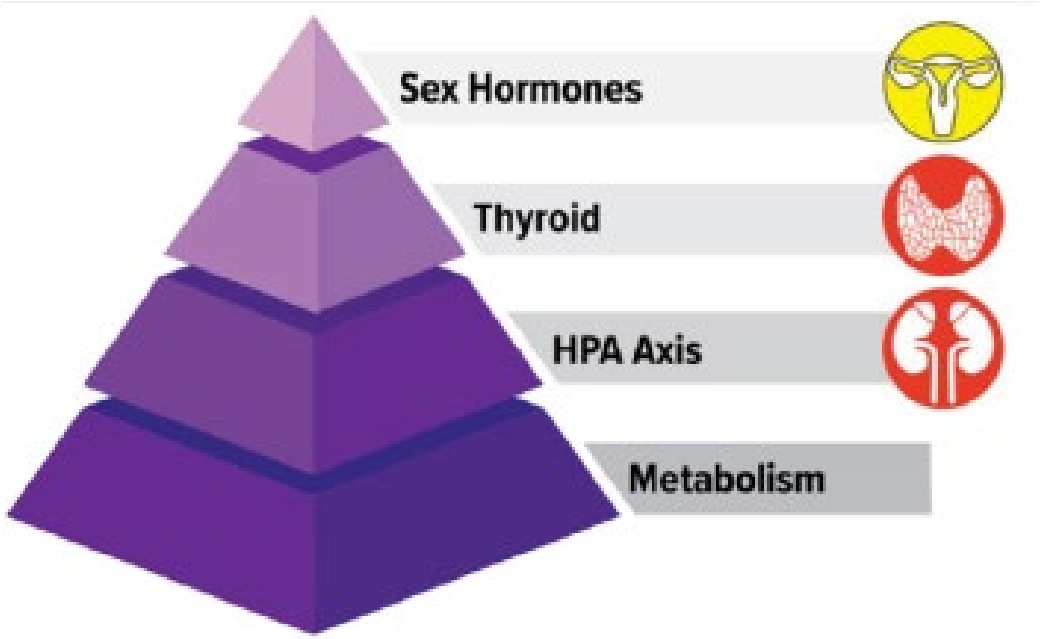


Endo+ reveals the complex interplay of hormones, not just their levels, providing essential insights for informed treatment and patient understanding.

GENOVA DIAGNOSTICS

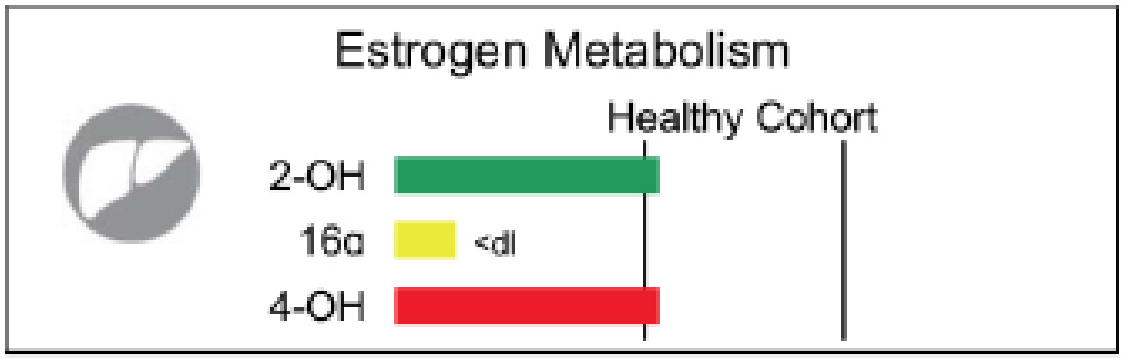
The Hormonal Pyramid in the Endo+

- Hormones influence each other
- Metabolic hormones (i.e. insulin) form the base of the pyramid and can impact other hormones
- The pyramid is bidirectional
- Colored circles next to the pyramid represent functional imbalance scores, indicating the relative need for therapeutic support:
  - Green: Low need for support
  - Grey: Optional need
  - Yellow: Moderate need
  - Red: High need for support
- Comprehensive hormone testing is helpful for identifying root causes of imbalance.
  - For instance, a patient with hypothyroidism might actually have an adrenal imbalance driving the thyroid issue.
  - Correcting the root cause (like an adrenal imbalance) might also correct other imbalances (like thyroid imbalance).
  - Both adrenal and thyroid imbalances can affect sex hormone levels
- Comprehensive panels are also helpful for identifying imbalances in multiple areas



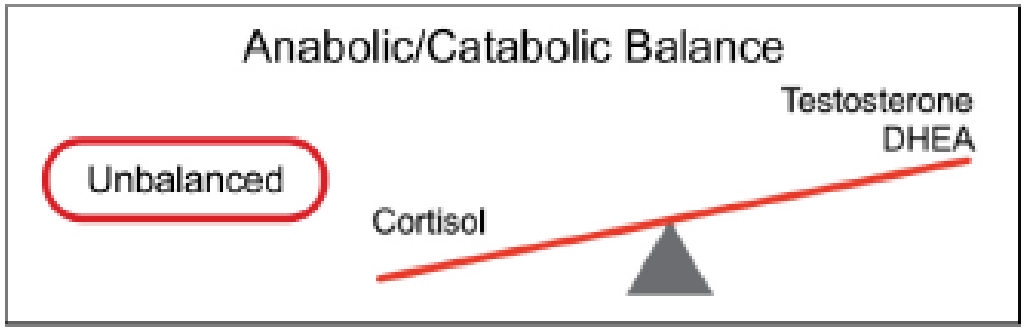
GENOVA DIAGNOSTICS

Estrogen Metabolism



The Estrogen Metabolism graphic shows whether a person is metabolizing parent estrogens into healthy or unhealthy metabolites. The horizontal green, yellow, and red bars show how close the results compare to a healthy cohort. 2-hydroxy estrogens (green) are generally considered favorable, whereas increased amounts of 16-alpha (yellow) and 4-hydroxy (red) estrogens tend to be associated with disease risk. These metabolites are often referred to as "the good, the bad, and the ugly", respectively. The information in this graphic will only be displayed if the urine estrogen assessment (Essential Estrogens) is ordered.

Anabolic Catabolic Balance



The Anabolic/Catabolic Balance graphic shows the ratio of total cortisol to testosterone and DHEA based on the percentiles of where they fall within their respective reference ranges. The analysis is similar to comparing the relative abundances of testosterone plus DHEA, and total cortisol. When you envision a balance scale, or see-saw, a side that is tipped lower means it is "heavier" in weight compared to the other hormones. For example, looking at the graphic above, cortisol is "heavier", meaning relatively higher compared to testosterone and DHEA. This imbalance is tipped in the direction favoring cortisol, suggesting a more catabolic state.

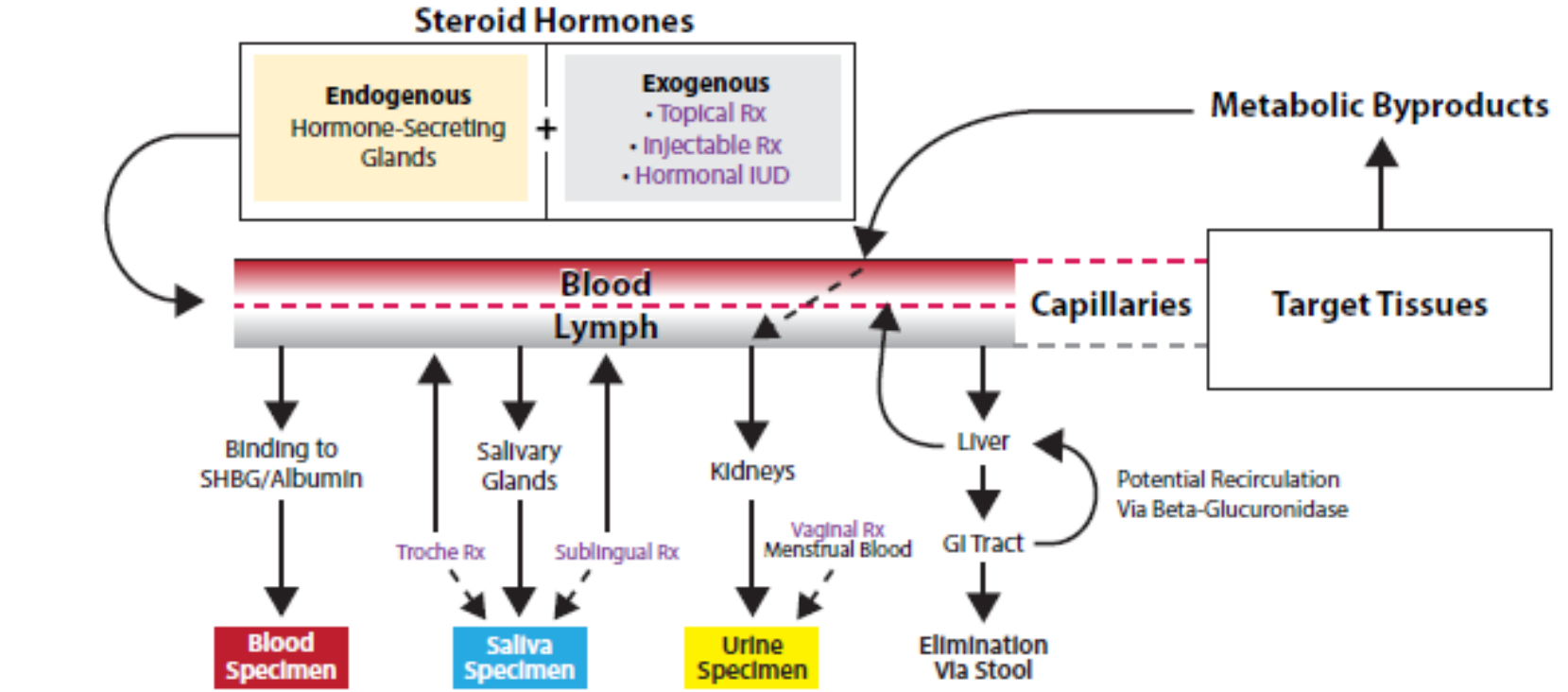
Cortisol has catabolic properties resulting in wear and tear, whereas testosterone and DHEA are anabolic and promote growth and repair. Excess cortisol can downregulate pathways that produce androgens, creating an imbalance. Adrenal support can be beneficial in balancing the ratio. Less often, the balance will favor the androgens, and this is usually a result of supplementation. There are no known negative consequences of relatively higher androgens with respect to cortisol. It is important to assess individual levels and treat them appropriately.

The information in this graphic will only be displayed if the Adrenocortex Stress Profile is ordered (cortisol, DHEA), and if testosterone is ordered in saliva.

Why Endo+ Stands Out

- **Unrivaled Comprehensive Evaluation**: The most thorough hormone assessment available
- **Modular Testing**: Build a personalized profile for each patient
- **Dynamic Reporting**: A synthesized view of hormonal interplay, enhancing patient care
- **Cost-Effective Solutions**: The more you add, the more you save, making comprehensive care accessible

Hormone Movements Pertinent to Specimen Type



	Blood Specimen	Saliva Specimen	Urine Specimen
Represents:	Total of bound and unbound levels	Unbound bioavailable levels	Unbound metabolites
Benefits:	• Widely utilized in conventional setting	• Ease of specimen collection • Ease of diurnal testing • Bioavailability	• Information about Estrogen metabolites and disease risk
Limitations:	• Binding to carrier/ transporter • Potential for under representation	• Not recommended if: - Troche or Sublingual Rx - Poor oral health -Salivary gland pathology	Not recommended if: - Abnormal kidney function - Vaginal Rx - Active menstruation

GENOVA DIAGNOSTICS

Genova's Endo+ Support Guide, 2024.

Choosing Sample Types

Serum Hormones	Salivary Hormones	Urinary Hormones
Assesses bound + unbound hormone (does include Free Androgen Index)	Assesses unbound, bioavailable hormone	Assesses unbound, bioavailable hormone
Patients taking transdermal hormones tend to have underrepresented levels	Patients taking transdermal hormones tend to have overrepresented levels (especially progesterone)	Effects of hormone therapies requires more research
Does not assess estrogen metabolism	Does not assess estrogen metabolism	Assesses estrogen metabolism to mitigate risk for hormone-related cancer
Requires a blood draw	Non-invasive, at-home collection	Non-invasive, at-home collection
Ability to assess SHBG	Does not assess SHBG	Does not assess SHBG
Bleeding gums do not affect sample integrity	Blood from the oral mucosa can contaminate the sample	Menstrual blood can contaminate samples

GENOVA DIAGNOSTICS

CORTISOL AWAKENING RESPONSE

GENOVA DIAGNOSTICS

REFERENCES

Smith	Smith, P., What You Must Know About Women's Hormones. 2nd Ed., Garden City Park, NY: Square One Publishers, 2022.
Smith	Smith, P., Maximize Your Male Hormones. Garden City Park, NY: Square One Publishers, 2023.
Smith	Smith, P., What You Must Know About Thyroid Disorders, 2nd Ed., Garden City Park, NY: Square One Publishers, 2024.

GENOVA DIAGNOSTICS

THE CORTISOL AWAKENING RESPONSE

- The cortisol awakening response (CAR) is an increase between 38% and 75% in cortisol levels peaking 30-45 minutes after awakening in the morning in some people.
- Evidence suggests the function of the CAR may be related to arousal, energy boost and/or anticipation. However, its precise function is not known.
- This rise is superimposed upon the late-night rise in cortisol which occurs before awakening.
  - Elder, Greg., et al., “"The cortisol awakening response – Applications and implications for sleep medicine,” Sleep Medicine Rev 2014; 18(3): 215–24.

THE CORTISOL AWAKENING RESPONSE (CONT.)

Cortisol is released from the adrenal glands after stimulation by ACTH release from the pituitary.

This occurs through the hypothalamus's production of corticotropin-releasing hormone (CRH). This production is subject to circadian rhythm and the day/night cycle.

Widmarier, E., et al., Vander's Human Physiology: The Mechanisms of Body Function (14th Ed.). New York, NY: McGraw Hill, 2016., p. 335.

THE CORTISOL AWAKENING RESPONSE (CONT.)

In the cortisol awakening response, the hypothalamic-pituitary-adrenal (HPA) axis is controlled by the hippocampus.

Therefore, the CAR is absent in the following situations:

- Bilateral and unilateral hippocampus damage
- Hippocampal atrophy
- Severe amnesia
- Presumed damage to the temporal lobe
- Absent temporal lobe
  - Wolf, O., et al., “No morning cortisol response in patients with severe global amnesia,” Psychoneuroendocrinology 2005; 30(1):101–05.

THE CORTISOL AWAKENING RESPONSE (CONT.)

- Patients with a larger hippocampus have a greater cortisol awakening response.
  - Pruessner, M., et al., "The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men," Psychiatry Res 2007; 155(1):1–10.

THE CORTISOL AWAKENING RESPONSE (CONT.)

- It is also possible that the suprachiasmatic nucleus, which is the light-sensitive biological clock, plays a role in regulation of the cortisol awakening response.
  - Fries, Eva., et al., “"The cortisol awakening response (CAR): Facts and future directions,” Inter Jour Psychophysiology 2009; 72(1): 67–73.

FUNCTION OF THE CORTISOL AWAKENING RESPONSE

- The function of the cortisol awakening response is not known.
- It may be linked with a stress-related preparation in regard to the upcoming day by the hippocampus.
  - Law, R., et al., "The cortisol awakening response predicts same morning executive function; results from a 50-day case study," Stress 2015; 18(6):616-21.

DIFFERENT RESPONSES

- Morning people show a larger cortisol awakening response than people who are not.
  - Kudielka, B., et al., "Morningness and eveningness: the free cortisol rise after awakening in ‘early birds’ and ‘night owls,’” Biol Psychol 2006; 72(2):141–46.

DIFFERENT RESPONSES (CONT.)

- The response is decreased with more pain that the patient is in.
  - Fabian, L., et al., “The association of the cortisol awakening response with experimental pain ratings,” Psychoneuroendocrinology 2009; 34(8):1247-51.

DIFFERENT RESPONSES (CONT.)

- If the patient has significant fatigue the cortisol response shows a low rise and flat plateau.
  - Kumari, M., et al., “Cortisol secretion and fatigue: associations in a community based cohort,” Psychoneuroendocrinology 2009; 34(10):1476-85.

DIFFERENT RESPONSES (CONT.)

The lower the individual's socioeconomic status, the higher their cortisol awakening response particularly in people as they age.

- Wright, C., et al., " "Subjective socioeconomic position, gender and cortisol responses to waking in an elderly population," Psychoneuroendocrinology 2005; 30(6):582–90.

A study showed that material hardship alters the diurnal rhythm of salivary cortisol.

- Ranjit, N., et al., "Material hardship alters the diurnal rhythm of salivary cortisol," Int Jour Epidemiol 2005; 34(5):1138-43.

GENOVA DIAGNOSTICS

STRESS

- The cortisol awakening response is increased when the patient wakes up on a day they are going to work versus a work-free day or work-free weekend.
  - Thorn, L., et al., “Suspected non-adherence and weekend versus week day differences in the awakening cortisol response,” Psychoneuroendocrinology 2006; 31(8):1009-18.
  - Schlotz, W., et al., “Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response,” Psychosom Med 2004; 66(2):207-14.

STRESS (CONT.)

- The response is increased when an individual is overloaded with work.
  - Steptoe, A., et al., "Job strain and anger expression predict early morning elevations in salivary cortisol," Psychosoma Med 2000; 62(2):286-92.

STRESS (CONT.)

- The response is increased when the stress is chronic.
  - Schlotz, W., et al., “Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response,” Psychosom Med 2004; 66(2):207-14.
  - Wust, S., et al., “Genetic factors, perceived chronic stress, and the free cortisol response to awakening,” Psychoneuroendocrinology 2000; 25(7):707-20.

STRESS (CONT.)

- Acute stress elevates the cortisol awakening response.
  - Rohleder, N., et al., “Stress o the dance floor: the cortisol stress response to social-evaluative threat in competitive ballroom dancers,” Pers Soc Psychol Bull 2007; 33(1):69-84.

STRESS (CONT.)

- When the patient is “burnt out” the cortisol awakening response can be high, low, or normal.
  - DeVente, W., et al., “Physiological differences between burnout patients and healthy controls: blood pressure, heart rate, and cortisol responses,” Occup Environ Med 2003; 60(Suppl 1):i54-61.
  - Pruessner, J., et al., “Burnout, perceived stress, and cortisol responses to awakening,” Psychosom Med 1999; 61(2):197-204.
  - Mommersteeg, P., et al., “Clinical burnout is not reflected in the cortisol awakening response,” the day-curve or the response to a low-dose dexamethasone suppression test,” Psychoneuroendocrinology 2006; 31(2):216-25.
  - Grossi, G., et al., “The morning salivary cortisol response in burnout,” Jour Psychosom Res 2005; 59(2):103-11.

SLEEP

- Waking up early drives up the cortisol awakening response.
  - Kudielka, B., et al., “Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase,” Psychoneuroendocrinology 2003; 28(1):35-47.

SLEEP (CONT.)

The cortisol awakening response only occurs after sleeping at night.

In the study the students taking a nap of 1-2 hours in the early evening from 6:45 pm to 8:30 pm had no response.

Federenko, I., et al., ""Free cortisol awakening responses are influenced by awakening time," Psychoneuroendocrinology. 2004; 29(2):174–84.

GENOVA DIAGNOSTICS

SLEEP (CONT.)

Shift work affects the cortisol awakening response.

Hospital works working on the morning shifts that got up between 4 am and 5:30 am had a greater and prolonged cortisol awakening response compared to those on the late day shift between 6 am and 9 am.

Federenko, I., et al., “"Free cortisol awakening responses are influenced by awakening time,” Psychoneuroendocrinology. 2004; 29(2):174–84.

SLEEP (CONT.)

- Another study revealed that the greater response may be due to stress and impaired sleep quality before an early morning shift.
  - Williams, E., et al., “The impact of time of waking and concurrent subjective stress on the cortisol response to awakening,” Psychoneuroendocrinology 2005; 30(2):139-48.

SLEEP (CONT.)

- Study showed that there was no rise in the level after nights with traffic-like low-frequency noise.
  - Waye, K., et al., “Effects of nighttime low frequency noise on the cortisol response to awakening and subjective sleep quality,” Life Sci 2003; 72:(8):863-75.

SLEEP (CONT.)

- The cortisol awakening response is higher when people wake up in light rather than darkness.
  - Scheer, F., et al., “Light affects morning salivary cortisol in humans,” Jour Clin Endocrinol metabol 1999; 84(9):3395-98.
  - Thorn, L., et al., “The effect of dawn simulation on the cortisol response to awakening in healthy participants, “ Psychoneuroendocrinology 2004; 29(7);925-30.

SLEEP (CONT.)

- Aspirin has been found to decrease the response due to its action upon ACTH.
  - Watson, S., et al., “Effect of aspirin on hypothalamic-pituitary-adrenal function and on neuropsychological performance in healthy adults: a pilot study,” Psychopharmacology 2009; 205(1):151-55.

SLEEP (CONT.)

- An alarm clock versus waking up spontaneously does not affect the cortisol awakening response.
  - Wust, S., et al., “The cortisol awakening response—normal values and confounds,” Noise Health 2000; 2(7):79-88.

NEUROPSYCHIATRY

- Studies have revealed that an elevated CAR is associated with major depression.
  - Holsboer, F., “Stress, hypercortisolism and corticosteroid receptors in depression: Implication for therapy,” Jour Affect Disord 2001; 80:125–33.
  - Van Santen A., et al., “Psychological traits and the cortisol awakening response: Results from the Netherland study of depression and anxiety,” Psychoneuroendocrinology 2001; 36:240–48.
  - Adam, E., et al., “Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence,” Psychoneuroendocrinology 2010; 35:921–31.

NEUROPSYCHIATRY (CONT.)

- An elevated cortisol awakening response has also been associated with anxiety disorders.
  - Mantella, R., et al., “Salivary cortisol is associated with diagnosis and severity of late life generalized anxiety disorder,” Psychoneuroendocrinology 2008; 33:773–81.
  - Vreeburg, S., et al., “Salivary cortisol levels in persons with and without different anxiety disorders,” Psychosom Med 2010; 72:340–47.

NEUROPSYCHIATRY (CONT.)

- One of the largest studies related to the cortisol awakening response showed that adults (average age of 44 years) with a diagnosis of depression or anxiety disorder had an elevated CAR.
  - Vreeburg, S., et al., "Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: Results from a large cohort study," Arch Gen Psychiatry Jour 2009; 66:617–26.

RELAPSING-REMITTING MULTIPLE SCLEROSIS

- Increased cortisol awaking response is associated with relapsing-remitting multiple sclerosis.
  - Kern, S., et al., “Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis,” Psychoneuroendocrinology 2011; 36:1505–12.

UPPER RESPIRATORY SYMPTOMS

- Elevated CRP is associated with upper respiratory symptoms.
  - Edwards, S., et al., “Components of the diurnal cortisol cycle in relation to upper respiratory symptoms and perceived stress,” Psychosom Med 2003; 65: 320–27.

VISCERAL OBESITY

- High cortisol awakening response has been found to be associated with visceral obesity.
  - Steptoe, A., et al., “Central adiposity and cortisol responses to waking in middle-aged men and women,” Int Jour Obes Relat Metab Disord 2004; 28:1168–73.

METABOLIC SYNDROME

- High cortisol awakening response is found in women with metabolic syndrome.
  - Bengtsson, I., et al., “The cortisol awakening response and the metabolic syndrome in a population-based sample of middle-aged men and women,” Metabolism 2010; 59:1012–19.

TYPE 2 DIABETES

- Low cortisol awakening response is associated with type 2 diabetes.
  - Bruehl, J., et al., “A blunted cortisol awakening response and hippocampal atrophy in type 2 diabetes mellitus,” Psychoneuroendocrinology2009; 34: 815–21.

CHRONIC FATIGUE SYNDROME

- Low CAR is associated with chronic fatigue syndrome.
  - Nater, U., et al., “Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls,” Jour Clin Endocrinol Metab 2008; 93:703–09.
  - Roberts, A., et al., “Salivary cortisol response to awakening in chronic fatigue syndrome,” Brit Jour Psychiatry 2004; 184: 136–41.

HYPERTENSION

- Low cortisol awakening response has been found to be associated with systemic hypertension.
  - Wirtz, P., et al., “Evidence for altered hypothalamus-pituitary-adrenal axis functioning in systemic hypertension: blunted cortisol response to awakening and lower negative feedback sensitivity,” Psychoneuroendocrinology 2007; 32:430–36.

GI DISORDERS

- Low cortisol awakening response is seen in functional GI disorders.
  - Bohmelt, A., et al., “Basal and stimulated hypothalamic-pituitary-adrenal axis activity in patients with functional gastrointestinal disorders and healthy controls,” 2005; 67:288–94.

CORTISOL AWAKENING RESPONSE

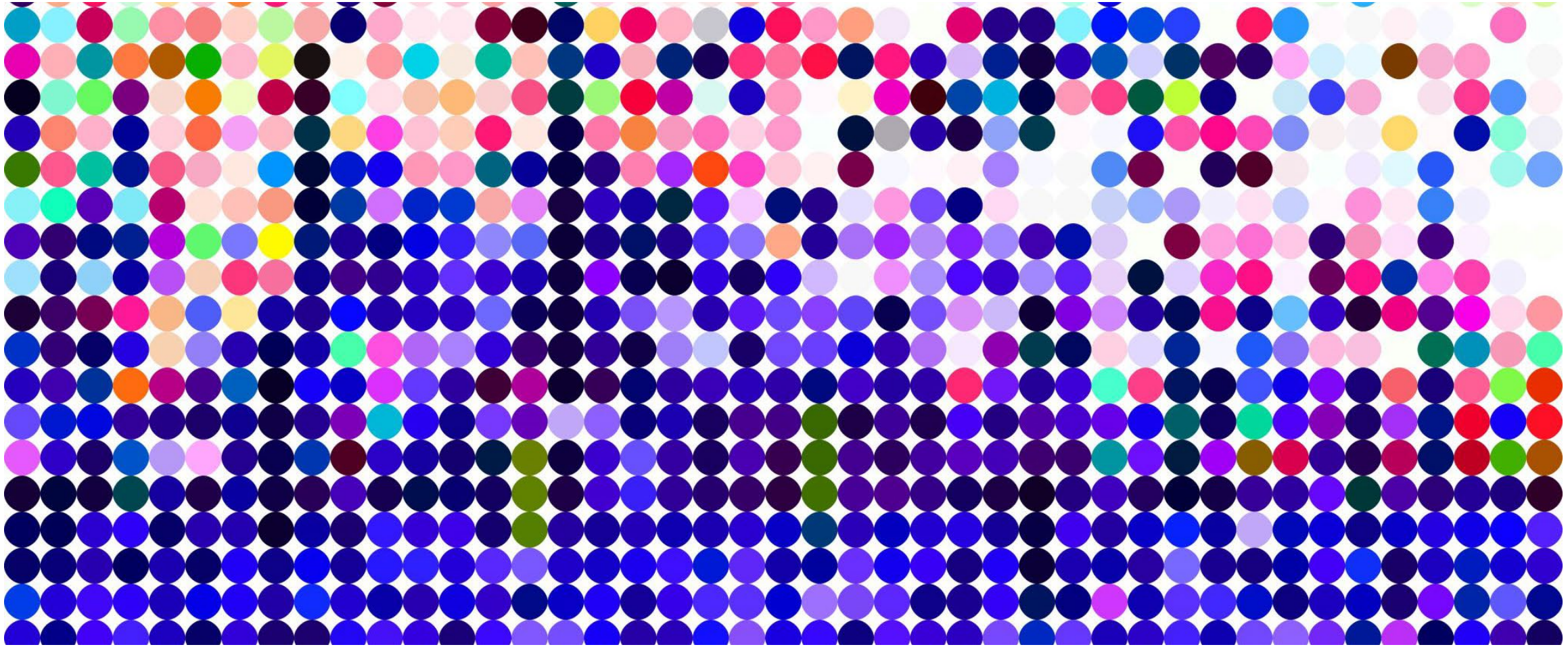
As you have seen, it is important to order a cortisol awakening response when you order salivary testing. Fortunately, it is part of the Endo+ test.

GENOVA DIAGNOSTICS

Case #1

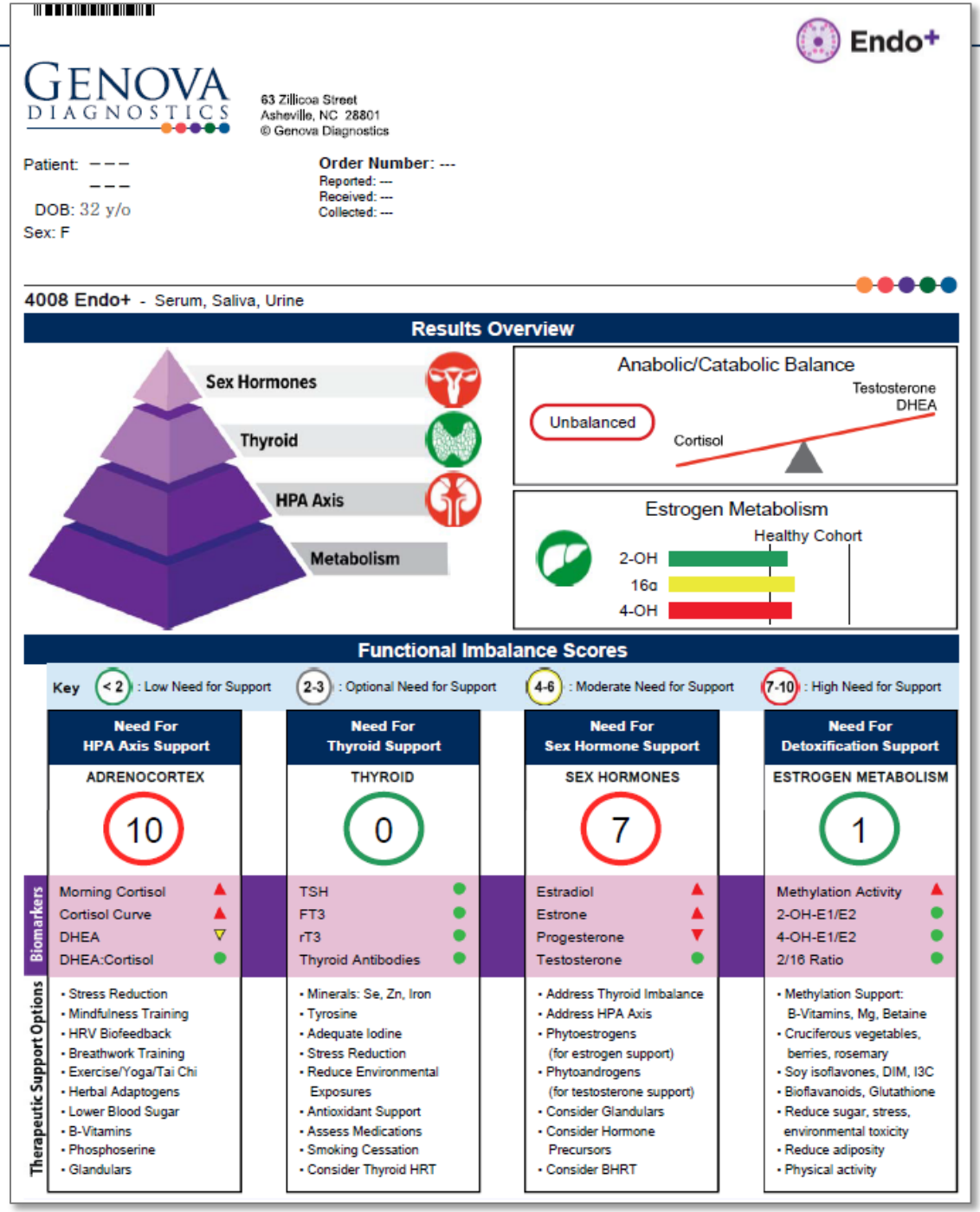
- This is a 32-year-old female with the chief complaint of weight gain.
- PH: unremarkable
- SH: employed as a computer analysist. She works for a company in England and therefore starts her workday at 4am every day. Patient has a poor diet. She rarely has breakfast and eats sugar throughout the day.
- FH: + mother has hypothyroidism. Father is hypertensive. Maternal grandmother died in a car accident at the age of 51. Maternal grandfather has heart disease. Paternal grandmother is healthy. Maternal grandfather has Parkinson's disease.
- Meds: none
- Vitamins: MVI, melatonin 3 mg qhs
- ROS: + anxiety and insomnia. Patient has some fatigue. Cycles are regular and every 28 days.

What Do You Want To Do With This Patient?



GENOVA DIAGNOSTICS

Case #1:
32 y/o female



GENOVA DIAGNOSTICS

63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Endo+

Patient: ---

DOB: 32 y/o
Sex: F

Order Number: ---
Reported: ---
Received: ---
Collected: ---

4008 Endo+ - Serum, Saliva, Urine

Results Overview

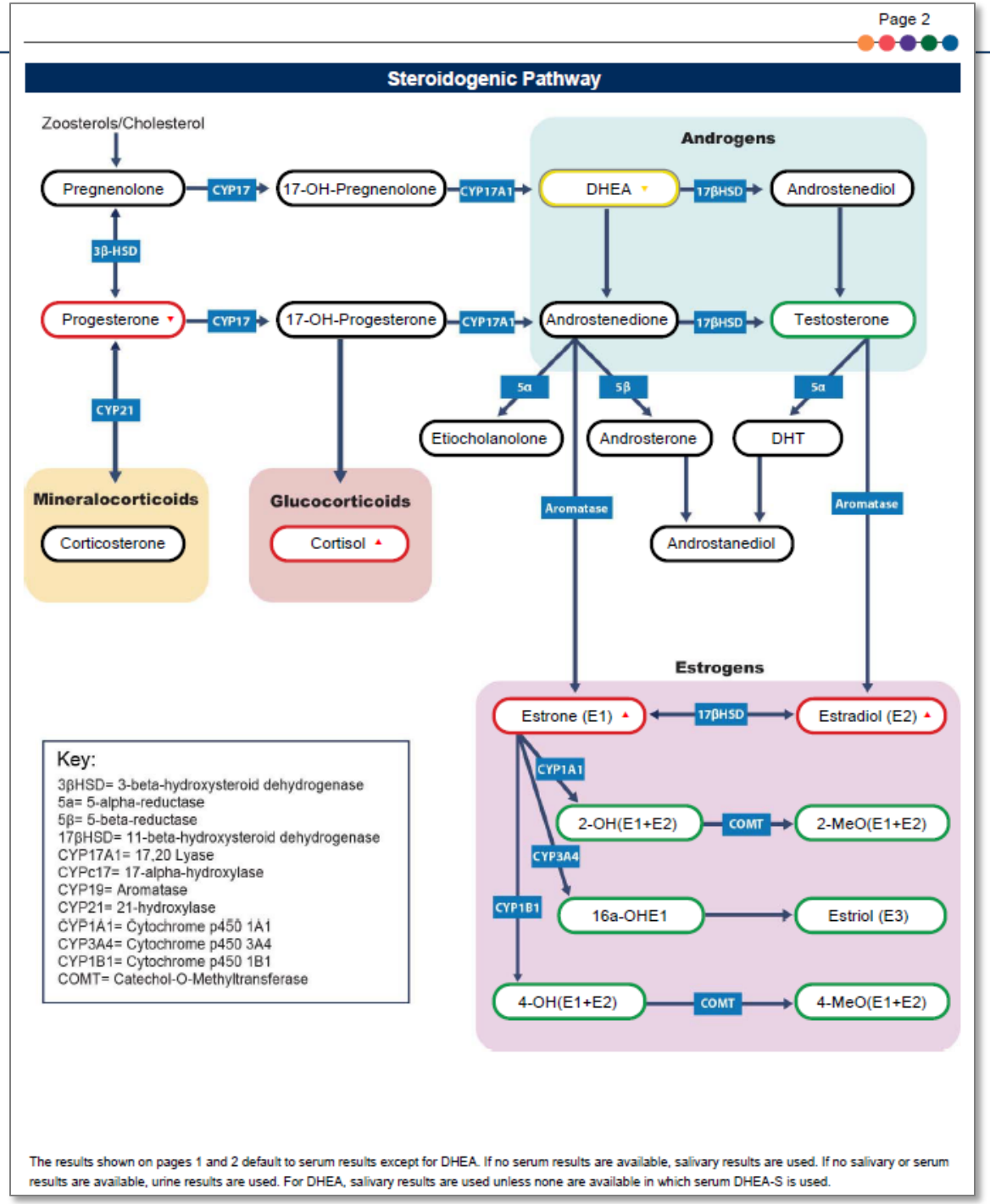
Functional Imbalance Scores

Key: <2 : Low Need for Support | 2-3 : Optional Need for Support | 4-6 : Moderate Need for Support | 7-10 : High Need for Support

	Need For HPA Axis Support	Need For Thyroid Support	Need For Sex Hormone Support	Need For Detoxification Support
	ADRENOCORTEX	THYROID	SEX HORMONES	ESTROGEN METABOLISM
	10	0	7	1
Biomarkers	Morning Cortisol ▲ Cortisol Curve ▲ DHEA ▽ DHEA:Cortisol ●	TSH ● FT3 ● rT3 ● Thyroid Antibodies ●	Estradiol ▲ Estrone ▲ Progesterone ▼ Testosterone ●	Methylation Activity ▲ 2-OH-E1/E2 ● 4-OH-E1/E2 ● 2/16 Ratio ●
Therapeutic Support Options	• Stress Reduction • Mindfulness Training • HRV Biofeedback • Breathwork Training • Exercise/Yoga/Tai Chi • Herbal Adaptogens • Lower Blood Sugar • B-Vitamins • Phosphoserine • Glandulars	• Minerals: Se, Zn, Iron • Tyrosine • Adequate Iodine • Stress Reduction • Reduce Environmental Exposures • Antioxidant Support • Assess Medications • Smoking Cessation • Consider Thyroid HRT	• Address Thyroid Imbalance • Address HPA Axis • Phytoestrogens (for estrogen support) • Phytoandrogens (for testosterone support) • Consider Glandulars • Consider Hormone Precursors • Consider BHRT	• Methylation Support: B-Vitamins, Mg, Betaine • Cruciferous vegetables, berries, rosemary • Soy isoflavones, DIM, I3C • Bioflavanoids, Glutathione • Reduce sugar, stress, environmental toxicity • Reduce adiposity • Physical activity

GENOVA DIAGNOSTICS

Case #1:
32 y/o female



GENOVA DIAGNOSTICS

Case #1:
32 y/o female

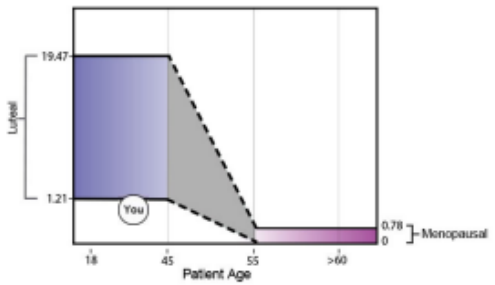
Endo+ Serum

Methodology: Chemiluminescent, RIA

Serum Sex Hormones

Progesterone

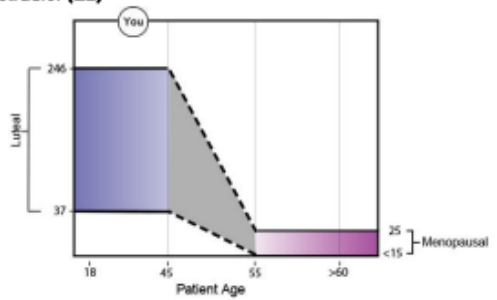
Progesterone



		Reference Range
Progesterone	1.05	See Chart Below

Estrogens

Estradiol (E2)



		Reference Range
Estradiol (E2)	267	See Chart Below
Estrone (E1)	313	43-250 pg/mL
Estriol (E3)	<80	<= 80 pg/mL

Androgens

		Reference Range
DHEA-S	96	23-266 mcg/dL
Testosterone, Total	0.53	<0.10-0.75 ng/mL
Free Androgen Index	2.38	0.43-8.48

Binding Proteins

		Reference Range
Sex Hormone Binding Globulin	77.1	18.2-135.5 nmol/L

Reference Range Information

Serum Analyte	Premenopause Luteal	Unsupplemented Menopause	Unsupplemented Male	Patient Result
Estrone (pg/mL)	43 - 250	18 - 63	46 - 143	313
Estradiol (pg/mL)	37 - 246	<15 - 25	<15 - 32	267
Estriol (pg/mL)	<=80	<=80	<=80	<80
Progesterone (ng/mL)	1.21 - 19.47	<=0.78	<=2.06	1.05
Testosterone (ng/mL)	<0.10 - 0.75	<0.10 - 0.75	1.75 - 7.81	0.53
Sex Hormone Binding Globulin (nmol/L)	18.2 - 135.5	16.8 - 125.2	13.3 - 89.5	77.1
Free Androgen Index	0.43 - 8.48	0.32 - 6.73	N/A	2.38

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.
The testosterone reference range is based on the manufacturer's range determined from women ages 21-73.

GENOVA DIAGNOSTICS

Case #1:
32 y/o female

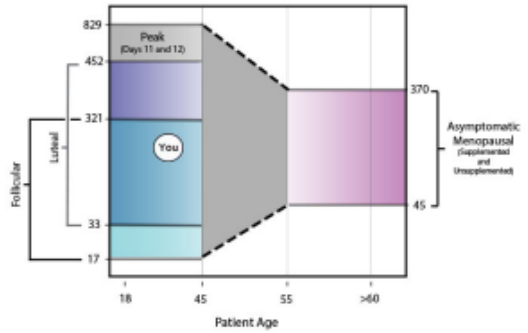
Endo+ Saliva

Methodology: EIA, LIA

Salivary Sex Hormones

Progesterone

Progesterone



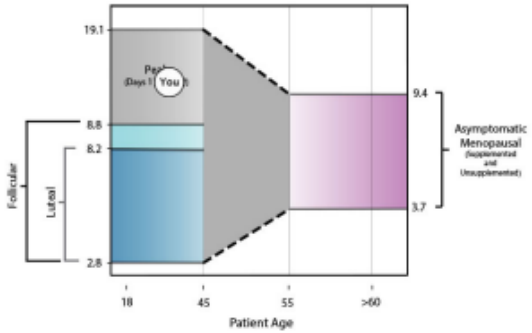
		Reference Range
Progesterone	224	See Chart Below

Androgens

DHEA ◆	171	71-640 pg/mL
Testosterone	<30	34-148 pmol/L

Estrogens

Estradiol (E2)



		Reference Range
Estradiol (E2)	11.4	See Chart Below
Estrone (E1) * ◆	127.3	31.9-183.4 pmol/L
Estriol (E3) * ◆	<70	<= 133 pmol/L

**Reference ranges for Estrone and Estriol are based on menopausal patients.*

Reference Range Information

Saliva Analyte	Luteal	Follicular	Menopausal	Male	Patient Result
Estrone (pmol/L)	N/A	N/A	31.9 - 183.4	N/A	127.3
Estradiol (pmol/L)	2.8 - 8.2	2.8 - 8.8	3.7 - 9.4	3.1 - 7.4	11.4
Estriol (pmol/L)	N/A	N/A	<=133	N/A	<70
Progesterone (pmol/L)	33 - 452	17 - 321	45 - 370	31 - 280	224
Testosterone (pmol/L)	34 - 148	34 - 148	34 - 148	110 - 513	<30
DHEA (pg/mL)	71 - 640	71 - 640	71 - 640	71 - 640	171

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

GENOVA DIAGNOSTICS

Case #1:
32 y/o female

Page 5

Endo+ Adrenocortex

Methodology: EIA

Adrenocortex

Diurnal Cortisol Curve

Cortisol Awakening Response

Cortisol Awakening Response

Percent Increase -12 Expected: >= 50 %

Cortisol, Free (Salivary)

		Reference Range
7AM-9AM Cortisol	0.373	0.097-0.337 mcg/dL
11AM-1PM Cortisol	0.087	0.027-0.106 mcg/dL
3PM-5PM Cortisol	0.198	0.013-0.068 mcg/dL
10PM-12PM Cortisol	0.049	<= 0.034 mcg/dL

Androgens

		Reference Range
DHEA	171	71-640 pg/mL
DHEA:Cortisol Ratio	458	358-2,538

Results

Cortisol, Free (Salivary)	Waking Cortisol	30 minutes	Morning Cortisol 7AM-9AM**	Midday Cortisol 11AM-1PM**	Afternoon Cortisol 3PM-5PM**	Evening Cortisol 10PM-12AM**
Patient Result (mcg/dL) >>	**0.706**	**0.622**	**0.373**	**0.087**	**0.198**	**0.049**
Reference Range (mcg/dL) **Based on Collection Times	N/A	N/A	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
Actual Collection Time	7:16AM	7:46AM	8:47AM	12:47PM	4:55PM	10:04PM

GENOVA DIAGNOSTICS

Case #1:
32 y/o female

Endo+ Urine

Methodology: LC/MS/MS

Estrogen Metabolism

Urine Estrogens

		Reference Range
Estrone (E1) ♦	21.2	2.0-26.2 mcg/g Creat.
Estradiol (E2) ♦	7.5	0.6-11.2 mcg/g Creat.
Estriol (E3) ♦	3.1	0.6-19.9 mcg/g Creat.

Phase 1 Estrogen Metabolites

		Reference Range
2-Hydroxyestrone+ ♦ 2-Hydroxyestradiol 2-OH(E1+E2)	8.3	1.3-36.3 mcg/g Creat.
16α-Hydroxyestrone ♦ 16α-OHE1	3.1	0.5-8.9 mcg/g Creat.
4-Hydroxyestrone+ ♦ 4-Hydroxyestradiol 4-OH(E1+E2)	1.6	<= 5.9 mcg/g Creat.

Enzyme Activity

2-OH(E1+E2)/ ♦ 16α-OHE1 Ratio	2.7	0.3-13.7
Methylation Activity ♦ 2-OH/2-MeO Ratio	1.3 (Poorer Methylation →)	1.6-10.7

Phase 2 Estrogen Metabolites

2-Methoxyestrone+ ♦ 2-Methoxyestradiol 2-MeO(E1+E2)	6.5	0.2-8.6 mcg/g Creat.
4-Methoxyestrone+ ♦ 4-Methoxyestradiol 4-MeO(E1+E2)	<dl	<= 1.0 mcg/g Creat.

Reference Range Information

Urine Analyte	Premenopause Luteal	Menopause	Male	Patient Result
Estrone (mcg/g Creat.)	2 - 26.2	1.1 - 26.2	1.6 - 8.6	21.2
Estradiol (mcg/g Creat.)	0.6 - 11.2	0.6 - 15.4	0.8 - 4.3	7.5
Estriol (mcg/g Creat.)	0.6 - 19.9	0.7 - 30.8	0.3 - 5.1	3.1
2-OH(E1+E2) (mcg/g Creat.)	1.3 - 36.3	0.9 - 43.8	0.7 - 12.5	8.3
16a-OHE1 (mcg/g Creat.)	0.5 - 8.9	0.4 - 7.7	<=2.0	3.1
4-OH(E1+E2) (mcg/g Creat.)	<=5.9	<=8.8	<=1.6	1.6
2-MeO(E1+E2) (mcg/g Creat.)	0.2 - 8.6	0.3 - 5.9	0.2 - 2.5	6.5
4-MeO(E1+E2) (mcg/g Creat.)	<=1.0	<=1.0	<=1.0	<dl
2-OH(E1+E2)/16a-OHE1 Ratio	0.3 - 13.7	0.3 - 15.1	0.8 - 12.9	2.7
2-OH/2-MeO Ratio	1.6 - 10.7	0.4 - 11.6	1.0 - 8.8	1.3

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

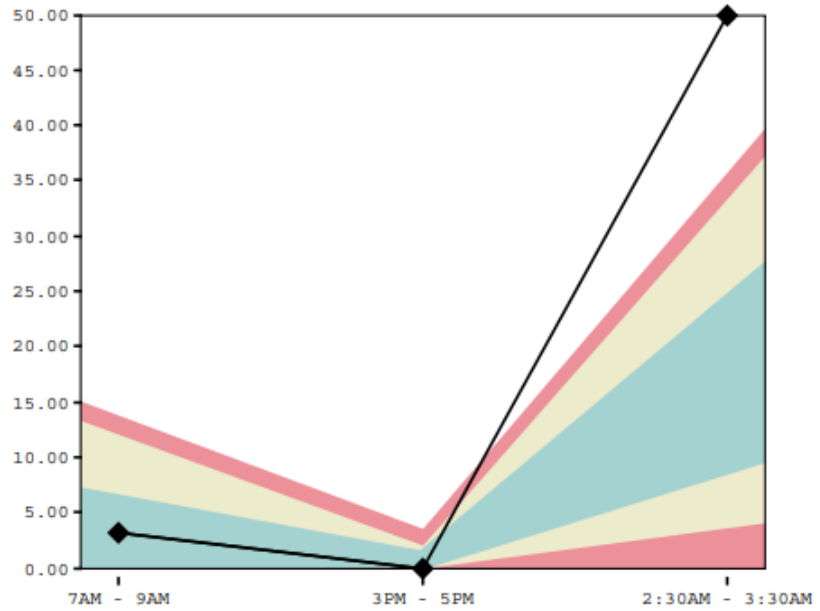
GENOVA DIAGNOSTICS

Case #1:
32 y/o female

Endo+ Melatonin

Methodology: EIA

Salivary Melatonin

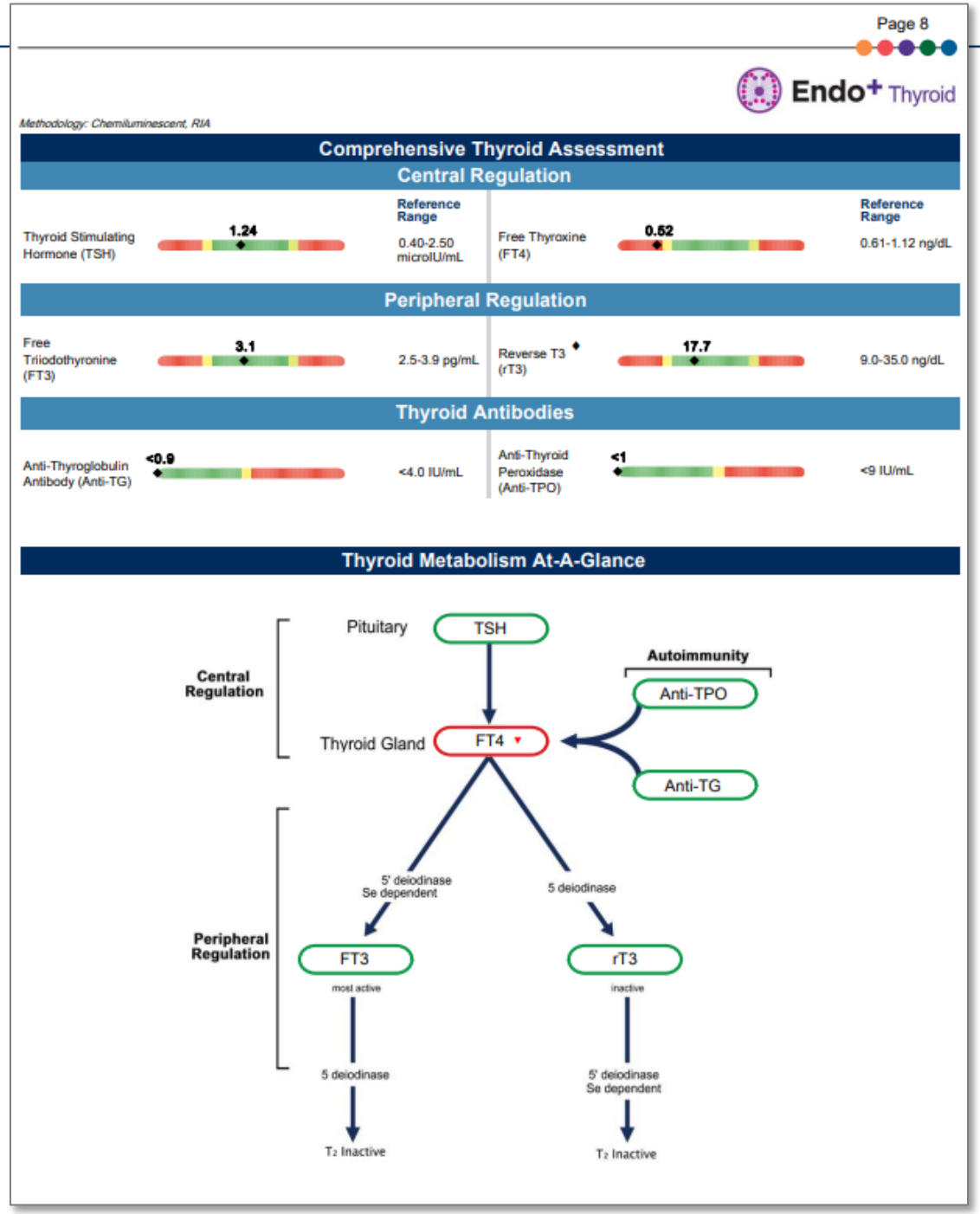


Results

Salivary Melatonin ♦	7AM-9AM**	3PM-5PM**	2:30AM-3:30AM**
Patient Result (pg/mL) >>	**3.23**	**<1.56**	**>50.00**
Reference Range (pg/mL) **Based on Collection Times	<=12.12	<=1.97	3.71-33.38

GENOVA DIAGNOSTICS

Case #1:
32 y/o female



Endo+ Thyroid

Methodology: Chemiluminescent, RIA

Comprehensive Thyroid Assessment

Central Regulation

		Reference Range			Reference Range
Thyroid Stimulating Hormone (TSH)	1.24	0.40-2.50 microIU/mL	Free Thyroxine (FT4)	0.52	0.61-1.12 ng/dL

Peripheral Regulation

Free Triiodothyronine (FT3)	3.1	2.5-3.9 pg/mL	Reverse T3 (rT3)	17.7	9.0-35.0 ng/dL

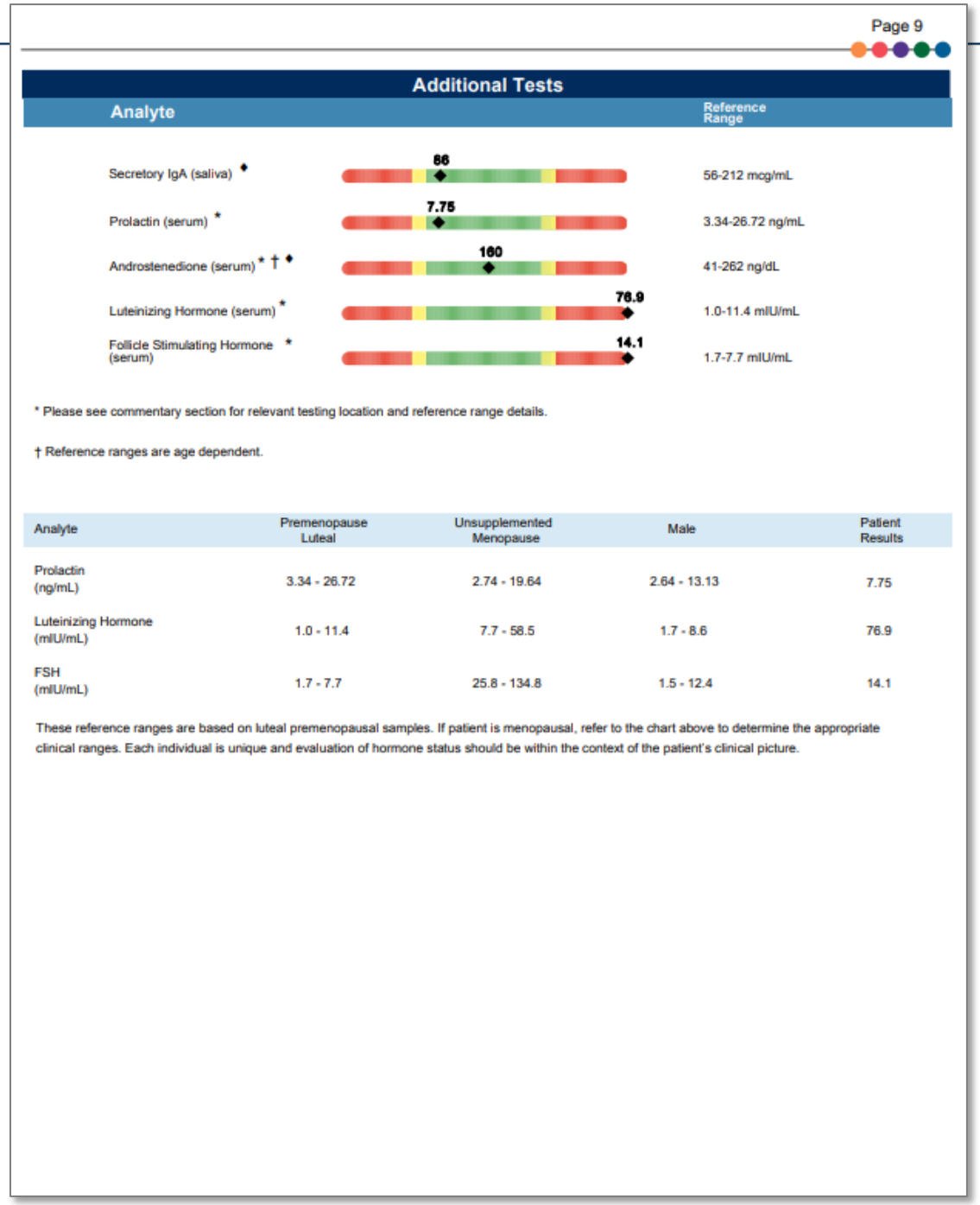
Thyroid Antibodies

Anti-Thyroglobulin Antibody (Anti-TG)	<0.9	<4.0 IU/mL	Anti-Thyroid Peroxidase (Anti-TPO)	<1	<9 IU/mL

Thyroid Metabolism At-A-Glance

GENOVA DIAGNOSTICS

Case #1:
32 y/o female



Additional Tests

Analyte		Reference Range
Secretory IgA (saliva) ♦	86	56-212 mcg/mL
Prolactin (serum) *	7.75	3.34-26.72 ng/mL
Androstenedione (serum) * † ♦	160	41-262 ng/dL
Luteinizing Hormone (serum) *	76.9	1.0-11.4 mIU/mL
Follicle Stimulating Hormone (serum) *	14.1	1.7-7.7 mIU/mL

* Please see commentary section for relevant testing location and reference range details.

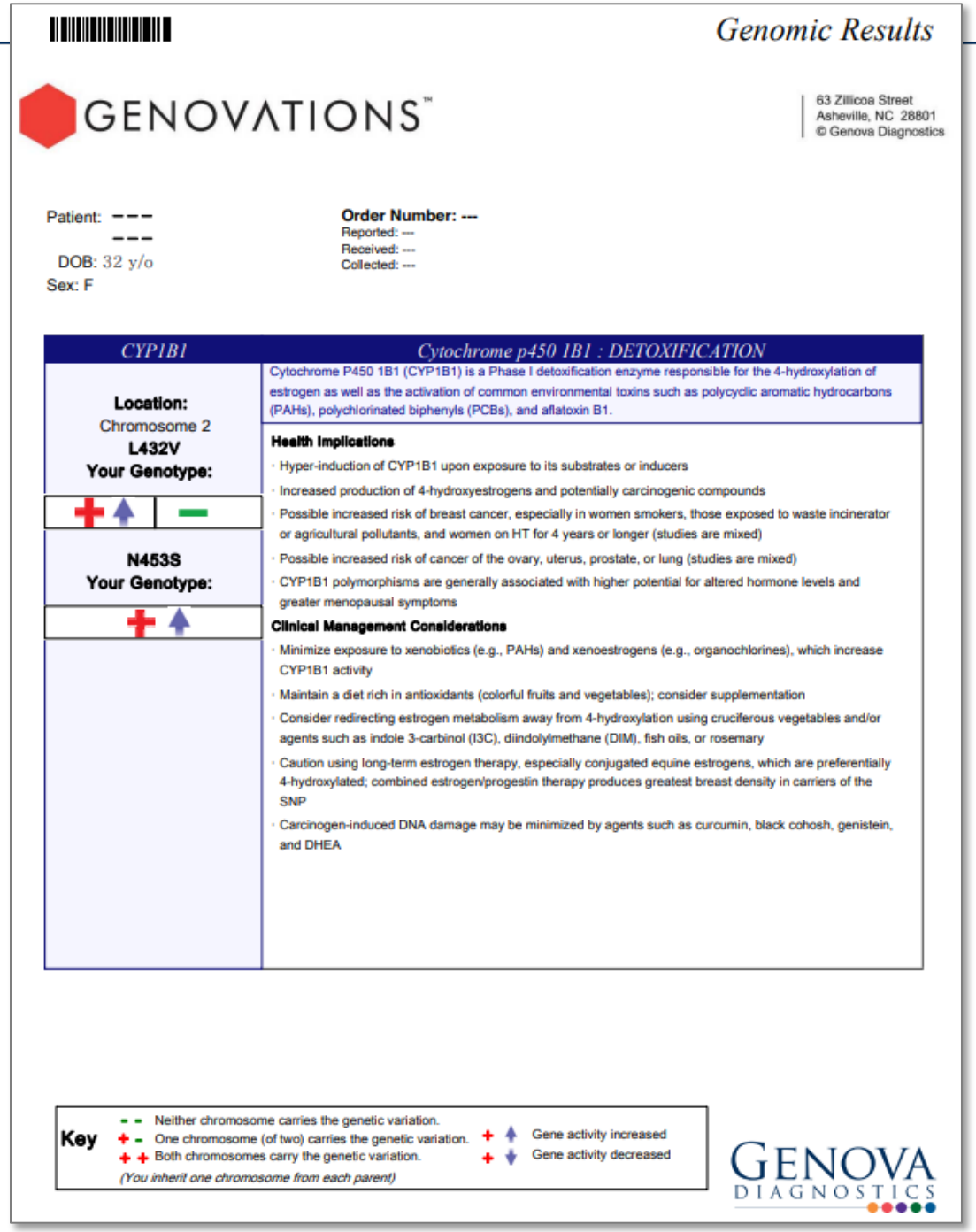
† Reference ranges are age dependent.

Analyte	Premenopause Luteal	Unsupplemented Menopause	Male	Patient Results
Prolactin (ng/mL)	3.34 - 26.72	2.74 - 19.64	2.64 - 13.13	7.75
Luteinizing Hormone (mIU/mL)	1.0 - 11.4	7.7 - 58.5	1.7 - 8.6	76.9
FSH (mIU/mL)	1.7 - 7.7	25.8 - 134.8	1.5 - 12.4	14.1

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

GENOVA DIAGNOSTICS

Case #1:
32 y/o female



Genomic Results

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Patient: ---

DOB: 32 y/o
Sex: F

Order Number: ---
Reported: ---
Received: ---
Collected: ---

CYP1B1	*Cytochrome p450 1B1 : DETOXIFICATION*
Location: Chromosome 2 **L432V** **Your Genotype:**	Cytochrome P450 1B1 (CYP1B1) is a Phase I detoxification enzyme responsible for the 4-hydroxylation of estrogen as well as the activation of common environmental toxins such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and aflatoxin B1. **Health Implications** · Hyper-induction of CYP1B1 upon exposure to its substrates or inducers · Increased production of 4-hydroxyestrogens and potentially carcinogenic compounds · Possible increased risk of breast cancer, especially in women smokers, those exposed to waste incinerator or agricultural pollutants, and women on HT for 4 years or longer (studies are mixed) · Possible increased risk of cancer of the ovary, uterus, prostate, or lung (studies are mixed) · CYP1B1 polymorphisms are generally associated with higher potential for altered hormone levels and greater menopausal symptoms **Clinical Management Considerations** · Minimize exposure to xenobiotics (e.g., PAHs) and xenoestrogens (e.g., organochlorines), which increase CYP1B1 activity · Maintain a diet rich in antioxidants (colorful fruits and vegetables); consider supplementation · Consider redirecting estrogen metabolism away from 4-hydroxylation using cruciferous vegetables and/or agents such as indole 3-carbinol (I3C), diindolylmethane (DIM), fish oils, or rosemary · Caution using long-term estrogen therapy, especially conjugated equine estrogens, which are preferentially 4-hydroxylated; combined estrogen/progestin therapy produces greatest breast density in carriers of the SNP · Carcinogen-induced DNA damage may be minimized by agents such as curcumin, black cohosh, genistein, and DHEA
N453S **Your Genotype:**	

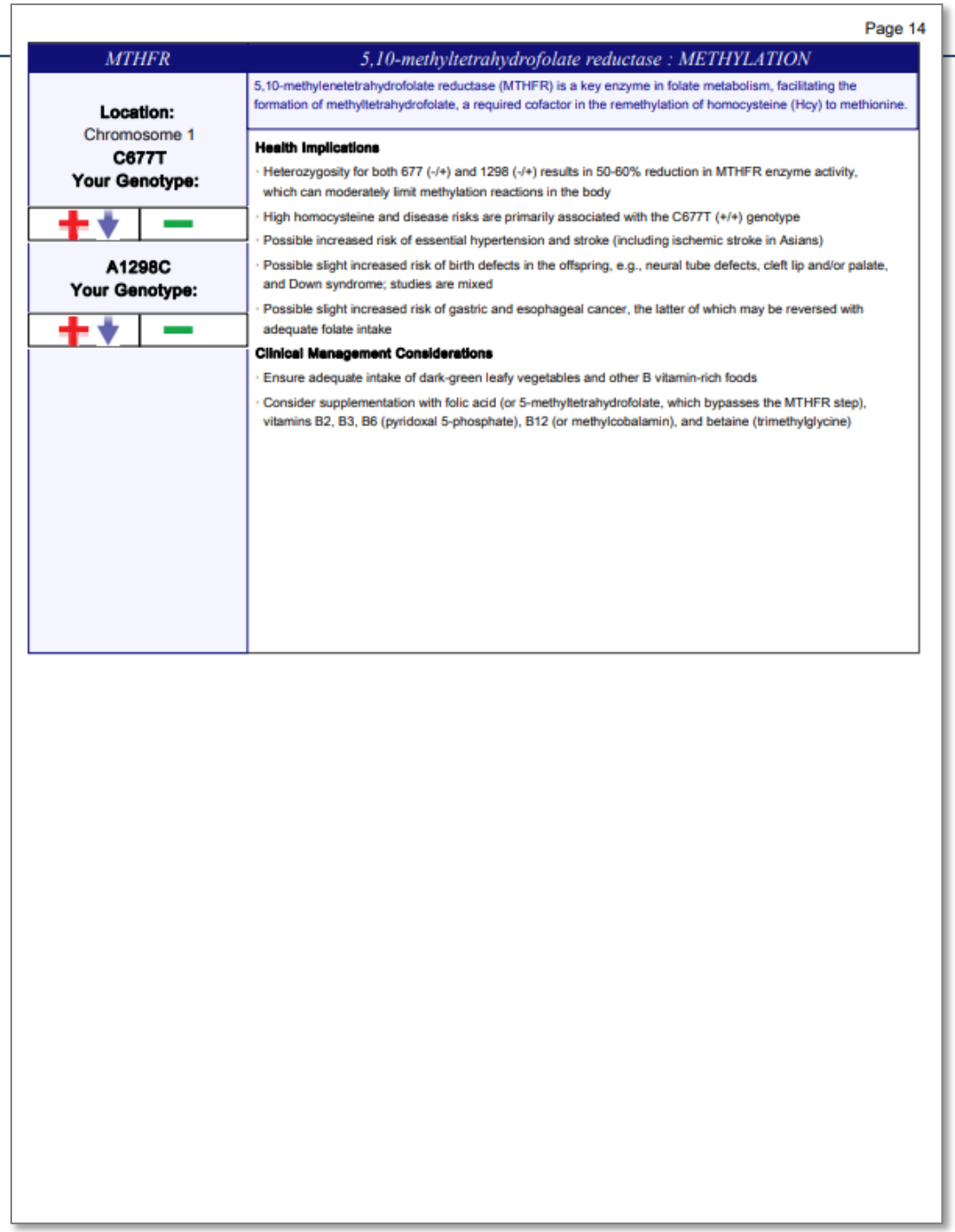
Key
- – Neither chromosome carries the genetic variation.
+ – One chromosome (of two) carries the genetic variation.
+ + Both chromosomes carry the genetic variation.
(You inherit one chromosome from each parent)

+ ↑ Gene activity increased
+ ↓ Gene activity decreased

GENOVA DIAGNOSTICS

GENOVA DIAGNOSTICS

Case #1:
32 y/o female

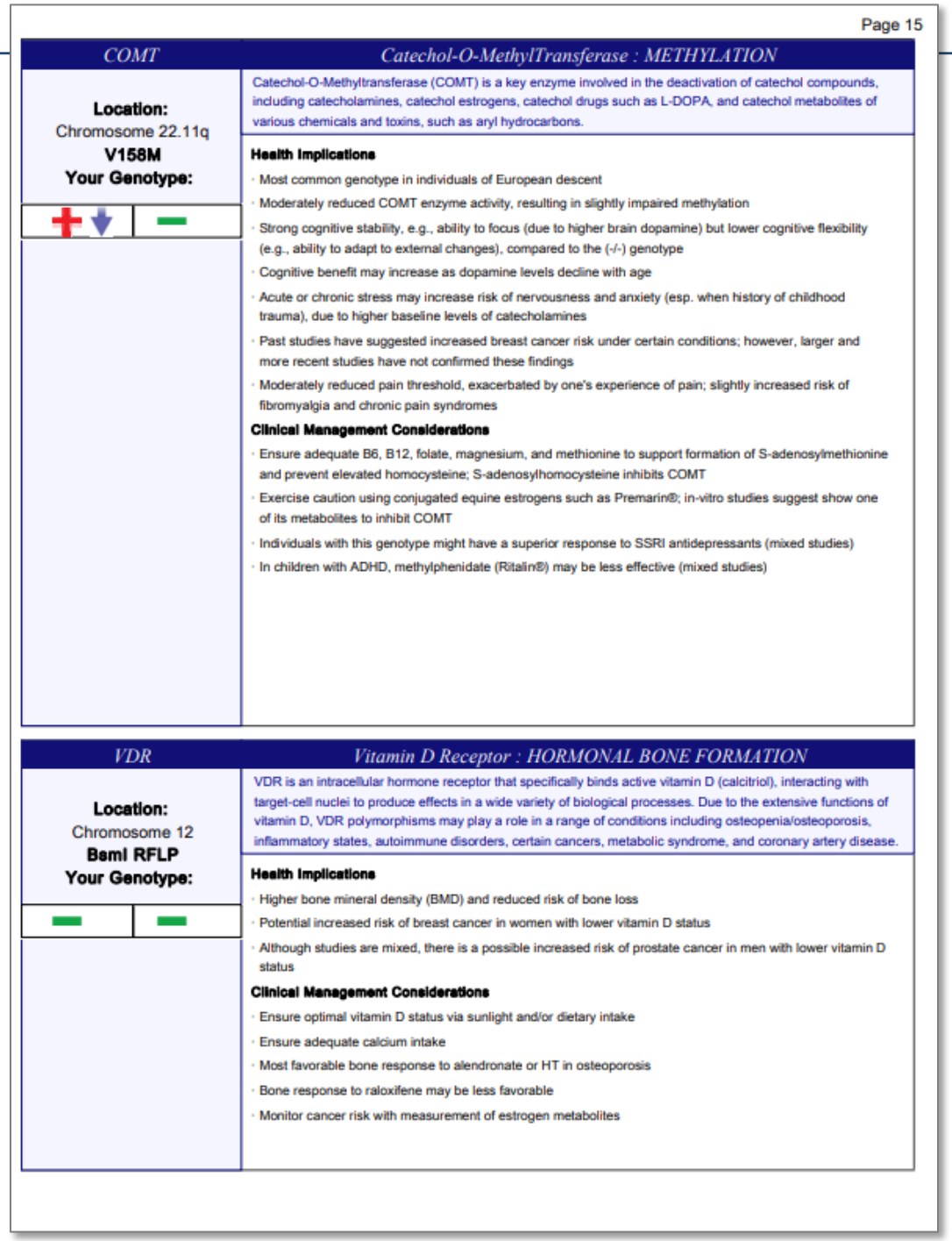


Page 14

MTHFR	5,10-methyltetrahydrofolate reductase : METHYLATION
Location: Chromosome 1 **C677T** **Your Genotype:** + / −	5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism, facilitating the formation of methyltetrahydrofolate, a required cofactor in the remethylation of homocysteine (Hcy) to methionine.
A1298C **Your Genotype:** + / −	**Health Implications** · Heterozygosity for both 677 (-/+) and 1298 (-/+) results in 50-60% reduction in MTHFR enzyme activity, which can moderately limit methylation reactions in the body · High homocysteine and disease risks are primarily associated with the C677T (+/+) genotype · Possible increased risk of essential hypertension and stroke (including ischemic stroke in Asians) · Possible slight increased risk of birth defects in the offspring, e.g., neural tube defects, cleft lip and/or palate, and Down syndrome; studies are mixed · Possible slight increased risk of gastric and esophageal cancer, the latter of which may be reversed with adequate folate intake **Clinical Management Considerations** · Ensure adequate intake of dark-green leafy vegetables and other B vitamin-rich foods · Consider supplementation with folic acid (or 5-methyltetrahydrofolate, which bypasses the MTHFR step), vitamins B2, B3, B6 (pyridoxal 5-phosphate), B12 (or methylcobalamin), and betaine (trimethylglycine)

GENOVA DIAGNOSTICS

Case #1:
32 y/o female



COMT — Catechol-O-MethylTransferase : METHYLATION

Location:
Chromosome 22.11q
V158M
Your Genotype:

Catechol-O-Methyltransferase (COMT) is a key enzyme involved in the deactivation of catechol compounds, including catecholamines, catechol estrogens, catechol drugs such as L-DOPA, and catechol metabolites of various chemicals and toxins, such as aryl hydrocarbons.

Health Implications

- Most common genotype in individuals of European descent
- Moderately reduced COMT enzyme activity, resulting in slightly impaired methylation
- Strong cognitive stability, e.g., ability to focus (due to higher brain dopamine) but lower cognitive flexibility (e.g., ability to adapt to external changes), compared to the (-/-) genotype
- Cognitive benefit may increase as dopamine levels decline with age
- Acute or chronic stress may increase risk of nervousness and anxiety (esp. when history of childhood trauma), due to higher baseline levels of catecholamines
- Past studies have suggested increased breast cancer risk under certain conditions; however, larger and more recent studies have not confirmed these findings
- Moderately reduced pain threshold, exacerbated by one's experience of pain; slightly increased risk of fibromyalgia and chronic pain syndromes

Clinical Management Considerations

- Ensure adequate B6, B12, folate, magnesium, and methionine to support formation of S-adenosylmethionine and prevent elevated homocysteine; S-adenosylhomocysteine inhibits COMT
- Exercise caution using conjugated equine estrogens such as Premarin®; in-vitro studies suggest show one of its metabolites to inhibit COMT
- Individuals with this genotype might have a superior response to SSRI antidepressants (mixed studies)
- In children with ADHD, methylphenidate (Ritalin®) may be less effective (mixed studies)

VDR — Vitamin D Receptor : HORMONAL BONE FORMATION

Location:
Chromosome 12
BsmI RFLP
Your Genotype:

VDR is an intracellular hormone receptor that specifically binds active vitamin D (calcitriol), interacting with target-cell nuclei to produce effects in a wide variety of biological processes. Due to the extensive functions of vitamin D, VDR polymorphisms may play a role in a range of conditions including osteopenia/osteoporosis, inflammatory states, autoimmune disorders, certain cancers, metabolic syndrome, and coronary artery disease.

Health Implications

- Higher bone mineral density (BMD) and reduced risk of bone loss
- Potential increased risk of breast cancer in women with lower vitamin D status
- Although studies are mixed, there is a possible increased risk of prostate cancer in men with lower vitamin D status

Clinical Management Considerations

- Ensure optimal vitamin D status via sunlight and/or dietary intake
- Ensure adequate calcium intake
- Most favorable bone response to alendronate or HT in osteoporosis
- Bone response to raloxifene may be less favorable
- Monitor cancer risk with measurement of estrogen metabolites

GENOVA DIAGNOSTICS

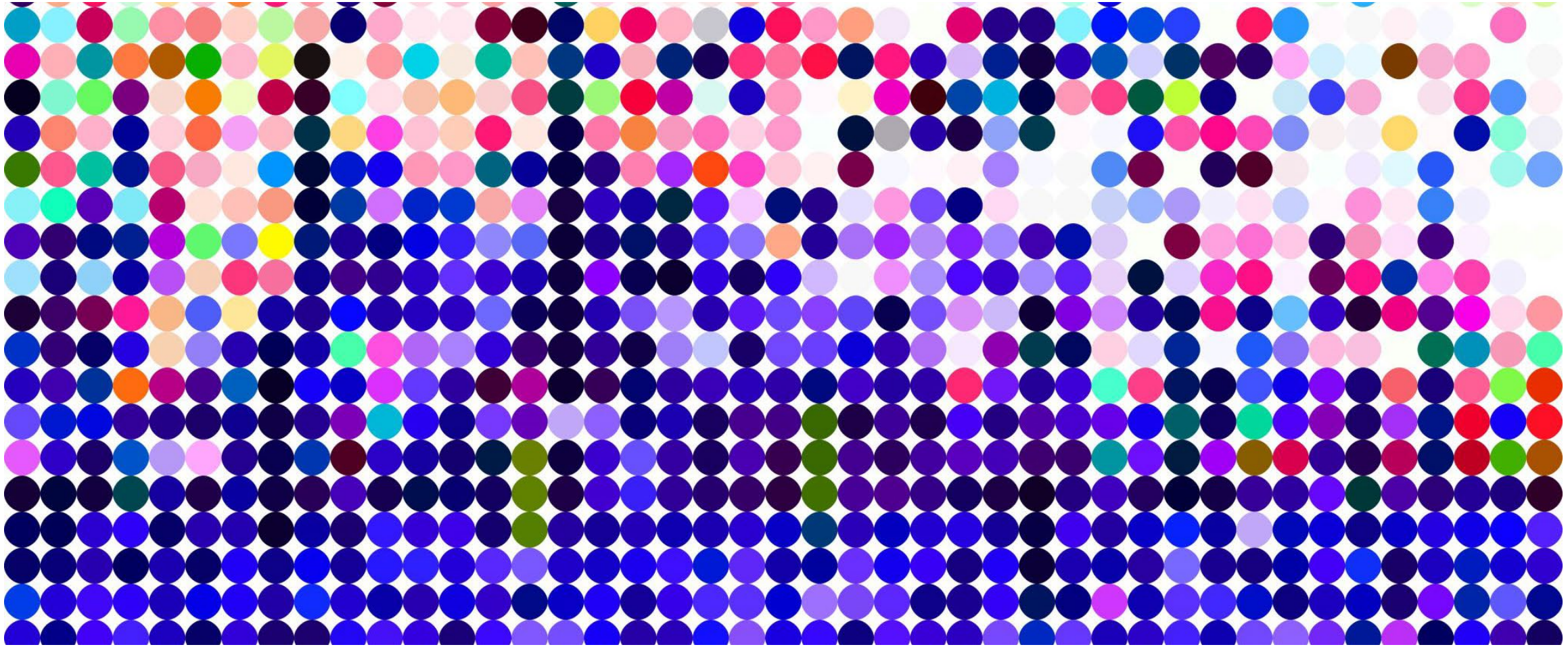
Case #1 (Cont.)

- Decrease estrogen with phase I (hydroxylation) and phase II (methylation and glucuronidation) pathways of detoxification of the liver. Hydroxylation yields three estrogen metabolites that vary greatly in activity: 2-hydroxyestrone (2-OH), 16-hydroxyestrone (16-OH), and 4-hydroxyestrone (4-OH). Phase III estrogen detoxification happens in the GI tract. Therefore, there is a link between estrogen dominance and gut health
- Start testosterone 1.0 mg cream.
- D/C melatonin.
- Start stress reduction techniques. Start adaptogenic herbs and calming herbs.
- Repeat FSH and LH and sex hormones by saliva in 3 months.
- Decrease sugar intake.

Case #2: 43 y/o female

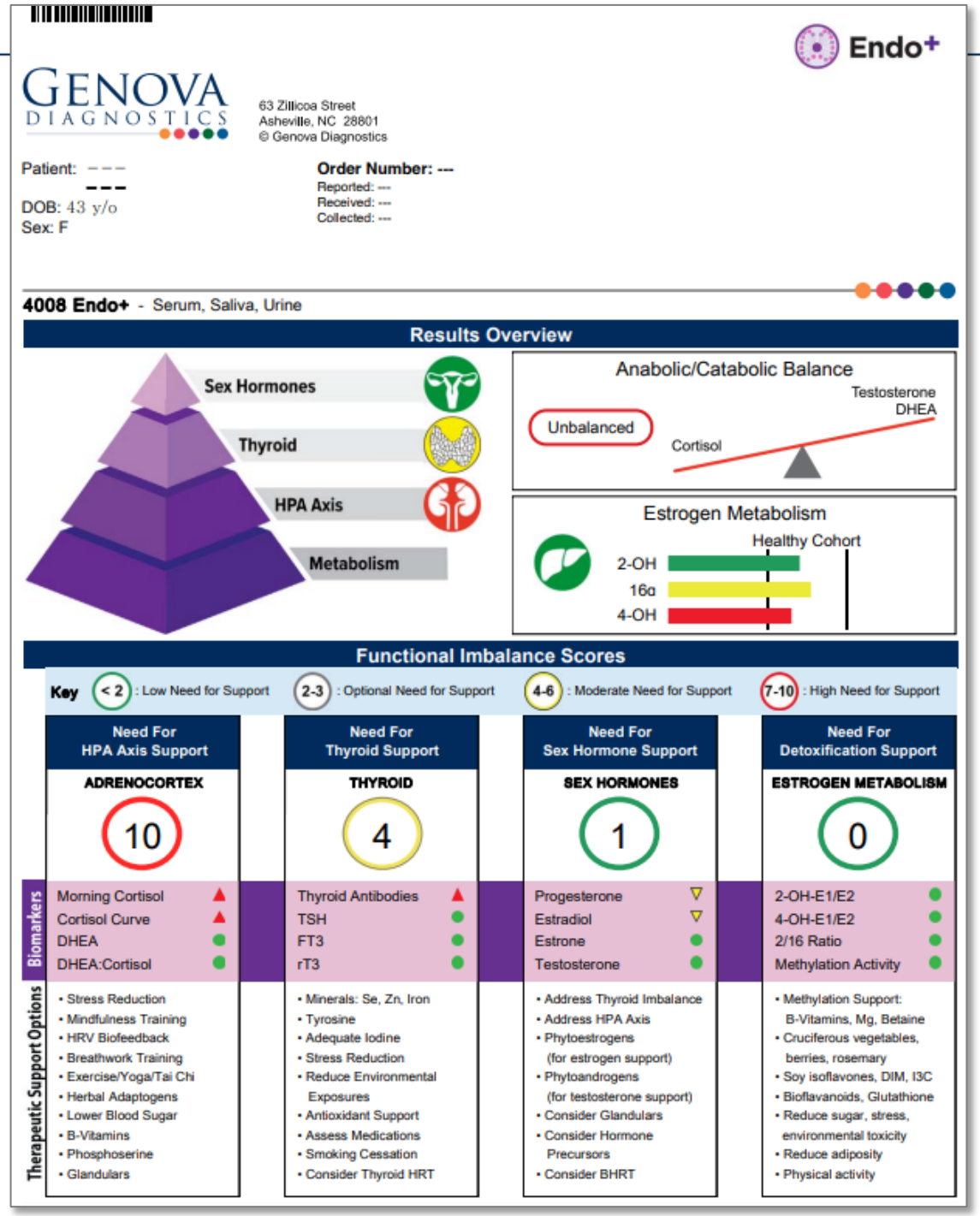
- This is a 43-year-old female who presents with fatigue. She has not felt well since she had COVID-19 three months ago.
- PH: COVID -19 three months ago. S/P right ankle surgery due to fracture at age 19 secondary to a skiing accident.
- SH: patient is a schoolteacher. Her husband is stationed overseas in the marines.
- FH: mother is healthy. Father has hypertension.
- Meds: none
- Vitamins: none
- ROS: unable to exercise vigorously since she had COVID.

What Do You Want To Do With This Patient?



GENOVA DIAGNOSTICS

Case #2:
43 y/o female



GENOVA DIAGNOSTICS

63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Endo+

Patient: ---

DOB: 43 y/o
Sex: F

Order Number: ---
Reported: ---
Received: ---
Collected: ---

4008 Endo+ - Serum, Saliva, Urine

Results Overview

Anabolic/Catabolic Balance

Estrogen Metabolism

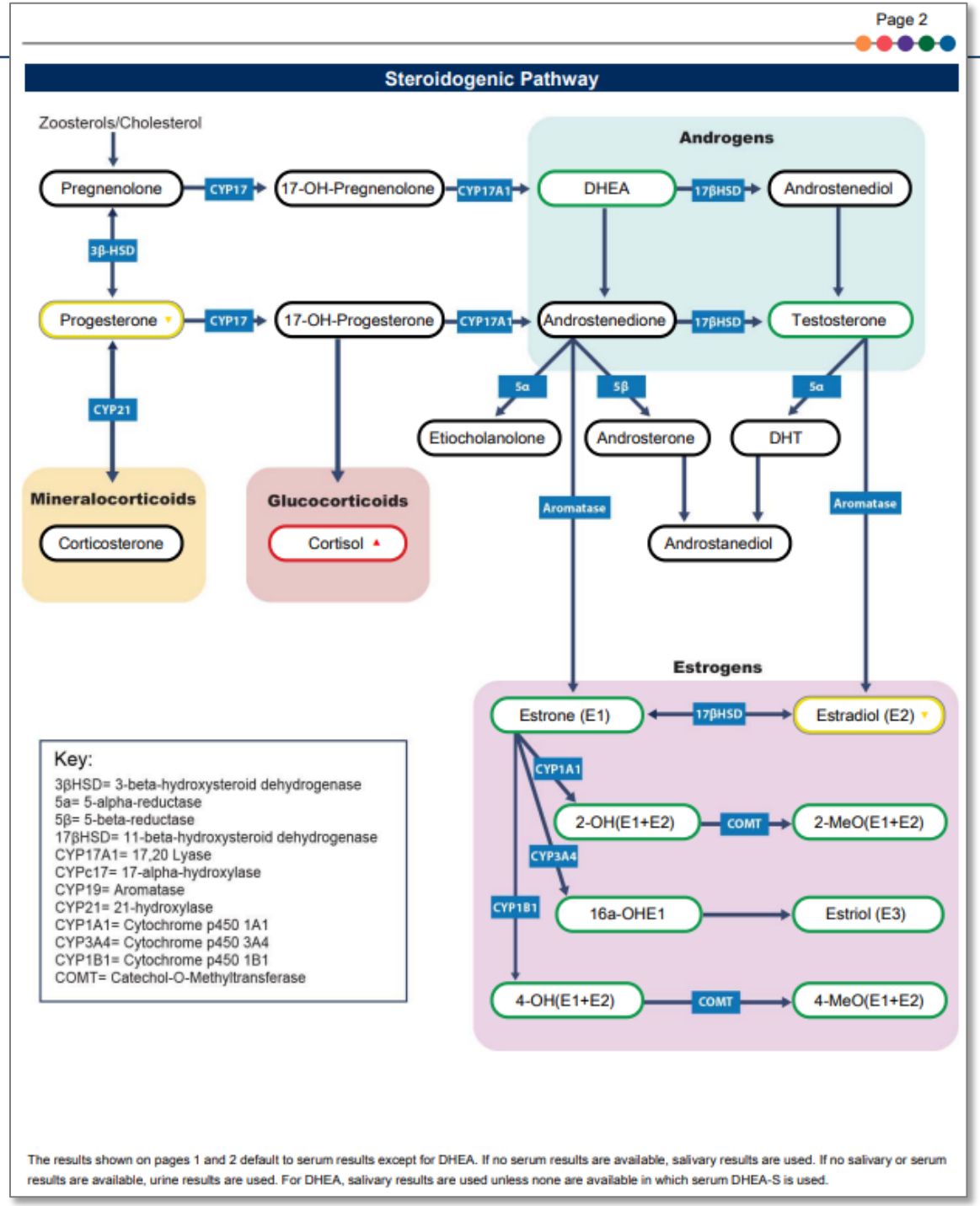
Functional Imbalance Scores

Key: < 2 : Low Need for Support | 2-3 : Optional Need for Support | 4-6 : Moderate Need for Support | 7-10 : High Need for Support

	Need For HPA Axis Support	Need For Thyroid Support	Need For Sex Hormone Support	Need For Detoxification Support
	ADRENOCORTEX	THYROID	SEX HORMONES	ESTROGEN METABOLISM
	10	4	1	0
Biomarkers	Morning Cortisol ▲ Cortisol Curve ▲ DHEA ● DHEA:Cortisol ●	Thyroid Antibodies ▲ TSH ● FT3 ● rT3 ●	Progesterone ▽ Estradiol ▽ Estrone ● Testosterone ●	2-OH-E1/E2 ● 4-OH-E1/E2 ● 2/16 Ratio ● Methylation Activity ●
Therapeutic Support Options	• Stress Reduction • Mindfulness Training • HRV Biofeedback • Breathwork Training • Exercise/Yoga/Tai Chi • Herbal Adaptogens • Lower Blood Sugar • B-Vitamins • Phosphoserine • Glandulars	• Minerals: Se, Zn, Iron • Tyrosine • Adequate Iodine • Stress Reduction • Reduce Environmental Exposures • Antioxidant Support • Assess Medications • Smoking Cessation • Consider Thyroid HRT	• Address Thyroid Imbalance • Address HPA Axis • Phytoestrogens (for estrogen support) • Phytoandrogens (for testosterone support) • Consider Glandulars • Consider Hormone Precursors • Consider BHRT	• Methylation Support: B-Vitamins, Mg, Betaine • Cruciferous vegetables, berries, rosemary • Soy isoflavones, DIM, I3C • Bioflavanoids, Glutathione • Reduce sugar, stress, environmental toxicity • Reduce adiposity • Physical activity

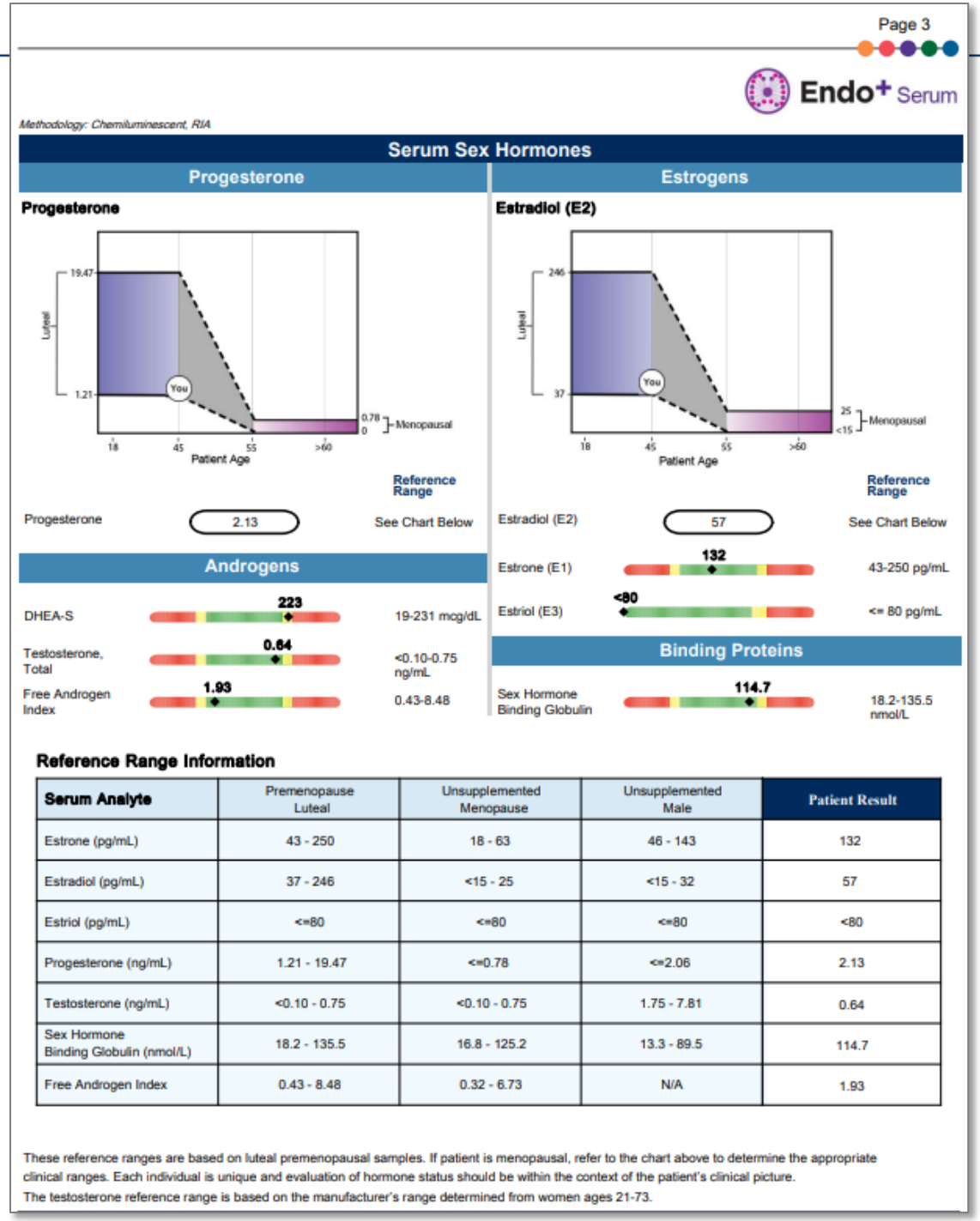
GENOVA DIAGNOSTICS

Case #2:
43 y/o female



GENOVA DIAGNOSTICS

Case #2:
43 y/o female



Endo+ Serum

Methodology: Chemiluminescent, RIA

Serum Sex Hormones

Progesterone

Progesterone

		Reference Range
Progesterone	2.13	See Chart Below

Estrogens

Estradiol (E2)

		Reference Range
Estradiol (E2)	57	See Chart Below
Estrone (E1)	132	43-250 pg/mL
Estriol (E3)	<80	<= 80 pg/mL

Androgens

DHEA-S	223	19-231 mcg/dL
Testosterone, Total	0.64	<0.10-0.75 ng/mL
Free Androgen Index	1.93	0.43-8.48

Binding Proteins

Sex Hormone Binding Globulin	114.7	18.2-135.5 nmol/L

Reference Range Information

Serum Analyte	Premenopause Luteal	Unsupplemented Menopause	Unsupplemented Male	Patient Result
Estrone (pg/mL)	43 - 250	18 - 63	46 - 143	132
Estradiol (pg/mL)	37 - 246	<15 - 25	<15 - 32	57
Estriol (pg/mL)	<=80	<=80	<=80	<80
Progesterone (ng/mL)	1.21 - 19.47	<=0.78	<=2.06	2.13
Testosterone (ng/mL)	<0.10 - 0.75	<0.10 - 0.75	1.75 - 7.81	0.64
Sex Hormone Binding Globulin (nmol/L)	18.2 - 135.5	16.8 - 125.2	13.3 - 89.5	114.7
Free Androgen Index	0.43 - 8.48	0.32 - 6.73	N/A	1.93

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.
The testosterone reference range is based on the manufacturer's range determined from women ages 21-73.

GENOVA DIAGNOSTICS

Case #2:
43 y/o female

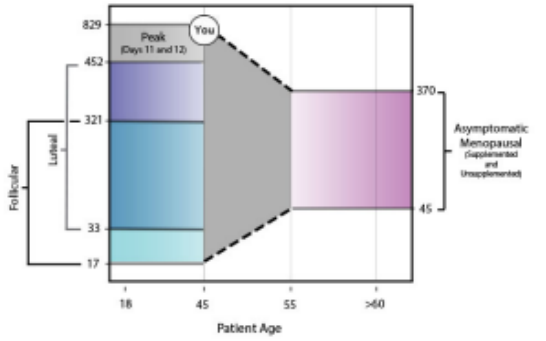
Endo+ Saliva

Methodology: EIA, LIA

Salivary Sex Hormones

Progesterone

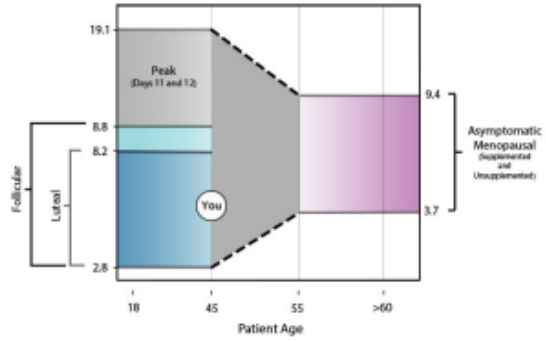
Progesterone



		Reference Range
Progesterone	780	See Chart Below

Estrogens

Estradiol (E2)



		Reference Range
Estradiol (E2)	4.2	See Chart Below
Estrone (E1) * ♦	77.3	31.9-183.4 pmol/L
Estriol (E3) * ♦	<70	<= 133 pmol/L

**Reference ranges for Estrone and Estriol are based on menopausal patients.*

Androgens

DHEA ♦	289	71-640 pg/mL
Testosterone	70	34-148 pmol/L

Reference Range Information

Saliva Analyte	Luteal	Follicular	Menopausal	Male	Patient Result
Estrone (pmol/L)	N/A	N/A	31.9 - 183.4	N/A	77.3
Estradiol (pmol/L)	2.8 - 8.2	2.8 - 8.8	3.7 - 9.4	3.1 - 7.4	4.2
Estriol (pmol/L)	N/A	N/A	<=133	N/A	<70
Progesterone (pmol/L)	33 - 452	17 - 321	45 - 370	31 - 280	780
Testosterone (pmol/L)	34 - 148	34 - 148	34 - 148	110 - 513	70
DHEA (pg/mL)	71 - 640	71 - 640	71 - 640	71 - 640	289

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

GENOVA DIAGNOSTICS

Case #2:
43 y/o female

Endo+ Adrenocortex

Methodology: EIA

Adrenocortex

Diurnal Cortisol Curve

Cortisol Awakening Response

Cortisol Awakening Response

Percent Increase 1,186 Expected: >= 50 %

Cortisol, Free (Salivary)

		Reference Range
7AM-9AM Cortisol	0.518	0.097-0.337 mcg/dL
11AM-1PM Cortisol	0.196	0.027-0.106 mcg/dL
3PM-5PM Cortisol	0.132	0.013-0.068 mcg/dL
10PM-12PM Cortisol	0.024	<= 0.034 mcg/dL

Androgens

		Reference Range
DHEA	269	71-640 pg/mL
DHEA:Cortisol Ratio	558	358-2,538

Results

Cortisol, Free (Salivary)	Waking Cortisol	30 minutes	Morning Cortisol 7AM-9AM**	Midday Cortisol 11AM-1PM**	Afternoon Cortisol 3PM-5PM**	Evening Cortisol 10PM-12AM**
Patient Result (mcg/dL) >>	**0.037**	**0.476**	**0.518**	**0.196**	**0.132**	**0.024**
Reference Range (mcg/dL) **Based on Collection Times	N/A	N/A	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
Actual Collection Time	3:35AM	4:05AM	7:42AM	12:42PM	4:55PM	10:03PM

GENOVA DIAGNOSTICS

Case #2:
43 y/o female

Endo+ Urine

Methodology: LC/MS/MS

Estrogen Metabolism

Urine Estrogens

		Reference Range
Estrone (E1) ♦	7.5	2.0-26.2 mcg/g Creat.
Estradiol (E2) ♦	3.2	0.6-11.2 mcg/g Creat.
Estriol (E3) ♦	7.2	0.6-19.9 mcg/g Creat.

Phase 1 Estrogen Metabolites

		Reference Range
2-Hydroxyestrone+ ♦ 2-Hydroxyestradiol 2-OH(E1+E2)	15.3	1.3-36.3 mcg/g Creat.
16α-Hydroxyestrone ♦ 16a-OHE1	5.0	0.5-8.9 mcg/g Creat.
4-Hydroxyestrone+ ♦ 4-Hydroxyestradiol 4-OH(E1+E2)	1.7	<= 5.9 mcg/g Creat.

Enzyme Activity

2-OH(E1+E2)/ ♦ 16α-OHE1 Ratio	3.1	0.3-13.7
Methylation Activity ♦ 2-OH/2-MeO Ratio	3.3	1.6-10.7

Poorer Methylation →

Phase 2 Estrogen Metabolites

2-Methoxyestrone+ ♦ 2-Methoxyestradiol 2-MeO(E1+E2)	4.6	0.2-8.6 mcg/g Creat.
4-Methoxyestrone+ ♦ 4-Methoxyestradiol 4-MeO(E1+E2)	<dl	<= 1.0 mcg/g Creat.

Reference Range Information

Urine Analyte	Premenopause Luteal	Menopause	Male	Patient Result
Estrone (mcg/g Creat.)	2 - 26.2	1.1 - 26.2	1.6 - 8.6	7.5
Estradiol (mcg/g Creat.)	0.6 - 11.2	0.6 - 15.4	0.8 - 4.3	3.2
Estriol (mcg/g Creat.)	0.6 - 19.9	0.7 - 30.8	0.3 - 5.1	7.2
2-OH(E1+E2) (mcg/g Creat.)	1.3 - 36.3	0.9 - 43.8	0.7 - 12.5	15.3
16a-OHE1 (mcg/g Creat.)	0.5 - 8.9	0.4 - 7.7	<=2.0	5.0
4-OH(E1+E2) (mcg/g Creat.)	<=5.9	<=8.8	<=1.6	1.7
2-MeO(E1+E2) (mcg/g Creat.)	0.2 - 8.6	0.3 - 5.9	0.2 - 2.5	4.6
4-MeO(E1+E2) (mcg/g Creat.)	<=1.0	<=1.0	<=1.0	<dl
2-OH(E1+E2)/16a-OHE1 Ratio	0.3 - 13.7	0.3 - 15.1	0.8 - 12.9	3.1
2-OH/2-MeO Ratio	1.6 - 10.7	0.4 - 11.6	1.0 - 8.8	3.3

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

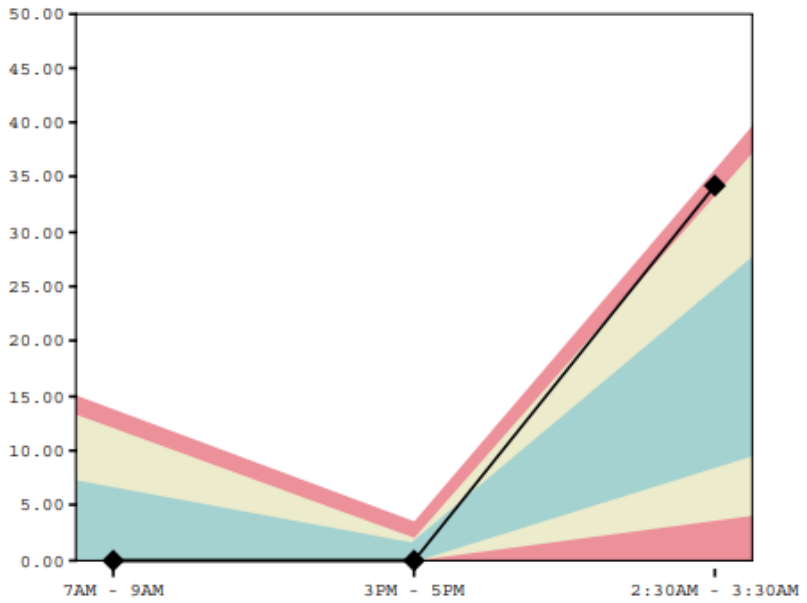
GENOVA DIAGNOSTICS

Case #2:
43 y/o female

Endo+ Melatonin

Methodology: EIA

Salivary Melatonin

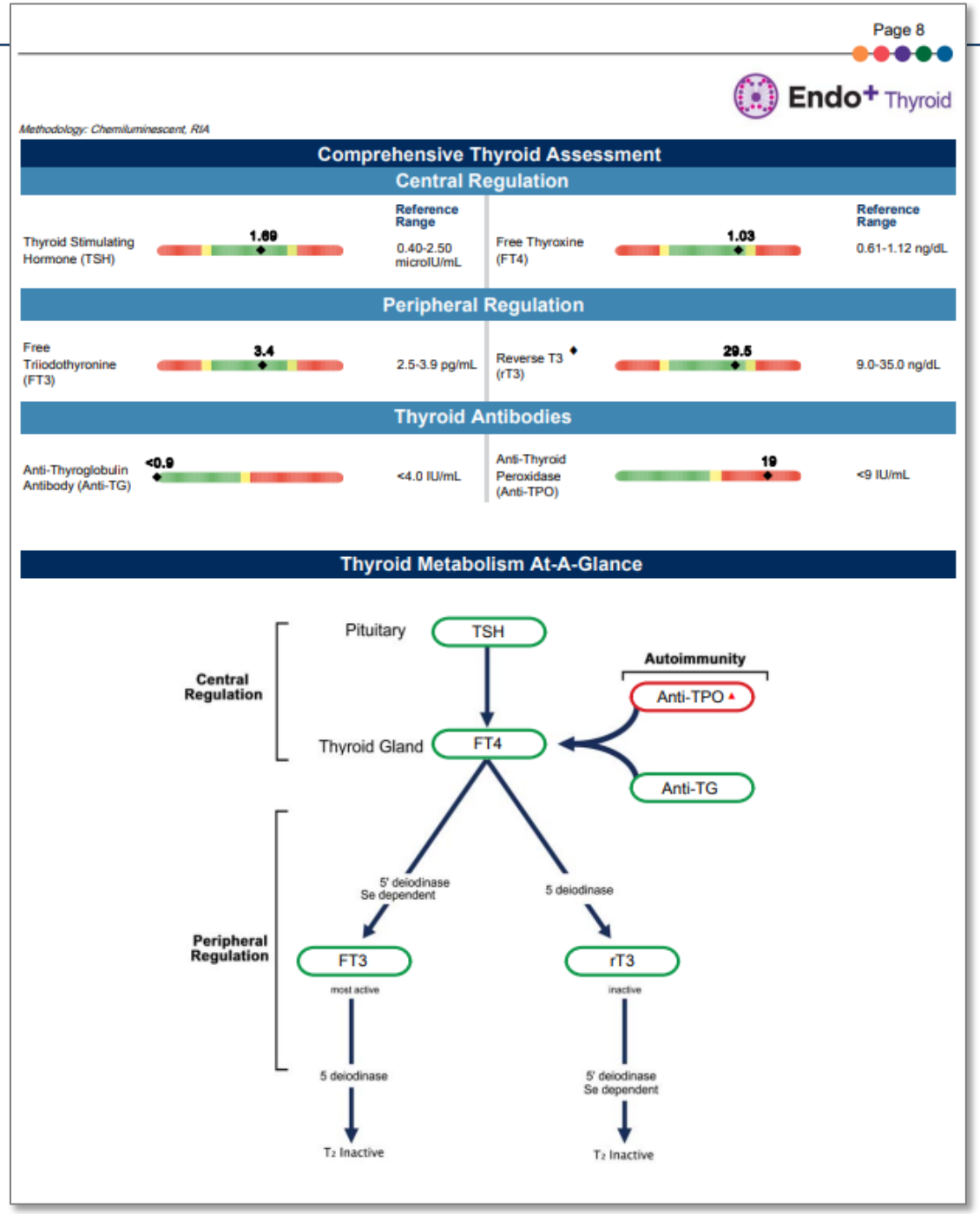


Results

Salivary Melatonin ♦	7AM-9AM**	3PM-5PM**	2:30AM-3:30AM**
Patient Result (pg/mL) >>	**<1.56**	**<1.56**	**34.17**
Reference Range (pg/mL) **Based on Collection Times	<=12.12	<=1.97	3.71-33.38

GENOVA DIAGNOSTICS

Case #2:
43 y/o female



Page 8

Endo+ Thyroid

Methodology: Chemiluminescent, RIA

Comprehensive Thyroid Assessment

Central Regulation

		Reference Range			Reference Range
Thyroid Stimulating Hormone (TSH)	1.69	0.40-2.50 microIU/mL	Free Thyroxine (FT4)	1.03	0.61-1.12 ng/dL

Peripheral Regulation

Free Triiodothyronine (FT3)	3.4	2.5-3.9 pg/mL	Reverse T3 (rT3)	29.5	9.0-35.0 ng/dL

Thyroid Antibodies

Anti-Thyroglobulin Antibody (Anti-TG)	<0.9	<4.0 IU/mL	Anti-Thyroid Peroxidase (Anti-TPO)	19	<9 IU/mL

Thyroid Metabolism At-A-Glance

GENOVA DIAGNOSTICS

Case #2:
43 y/o female

Additional Tests

Analyte		Reference Range
Secretory IgA (saliva) ♦	146	56-212 mcg/mL
Prolactin (serum) *	13.98	3.34-26.72 ng/mL
Androstenedione (serum) * † ♦	88	41-262 ng/dL
Luteinizing Hormone (serum) *	3.5	1.0-11.4 mIU/mL
Follicle Stimulating Hormone (serum) *	4.2	1.7-7.7 mIU/mL

* Please see commentary section for relevant testing location and reference range details.

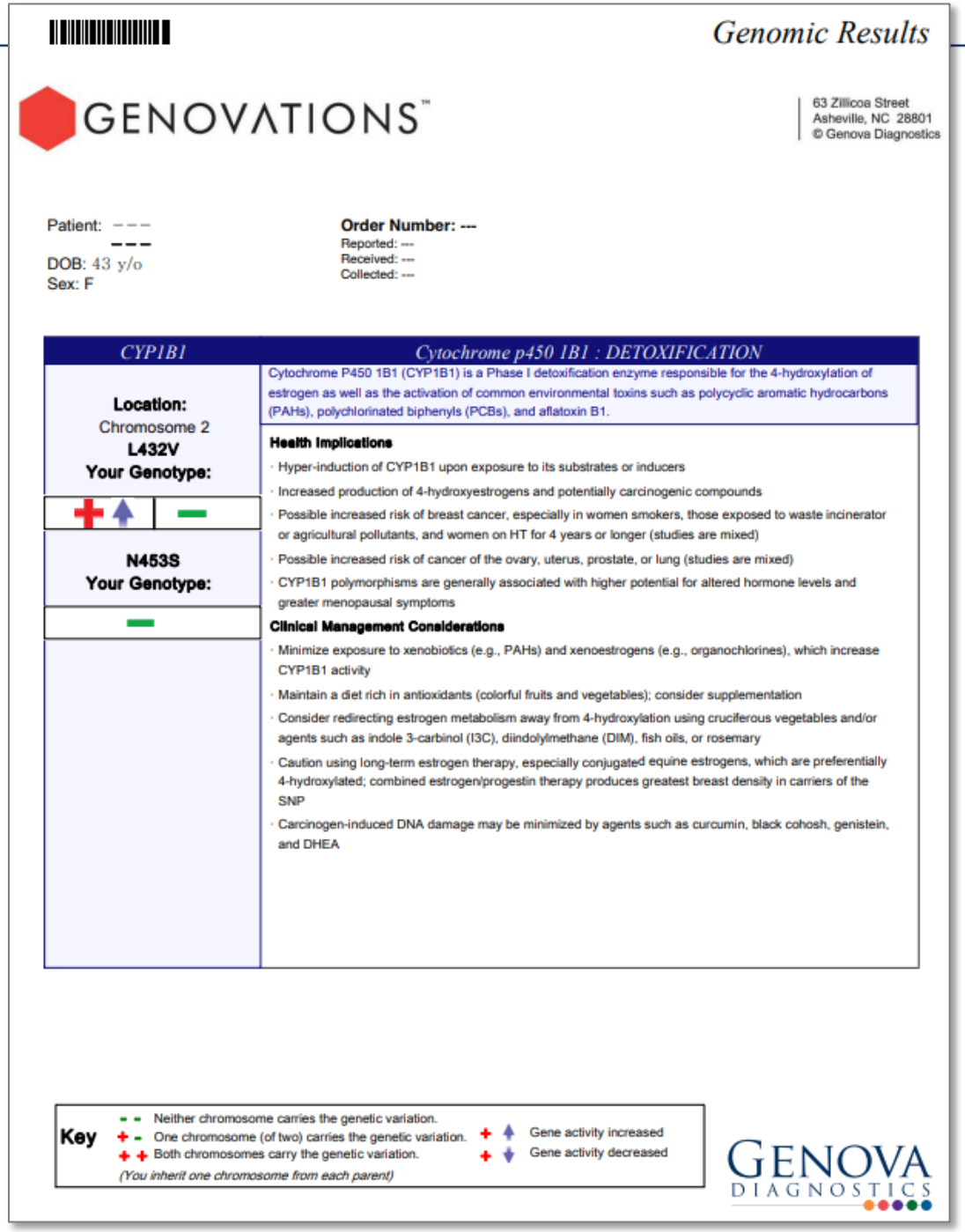
† Reference ranges are age dependent.

Analyte	Premenopause Luteal	Unsupplemented Menopause	Male	Patient Results
Prolactin (ng/mL)	3.34 - 26.72	2.74 - 19.64	2.64 - 13.13	13.98
Luteinizing Hormone (mIU/mL)	1.0 - 11.4	7.7 - 58.5	1.7 - 8.6	3.5
FSH (mIU/mL)	1.7 - 7.7	25.8 - 134.8	1.5 - 12.4	4.2

These reference ranges are based on luteal premenopausal samples. If patient is menopausal, refer to the chart above to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

GENOVA DIAGNOSTICS

Case #2:
43 y/o female



Genomic Results

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Patient: ---

DOB: 43 y/o
Sex: F

Order Number: ---
Reported: ---
Received: ---
Collected: ---

CYP1B1	Cytochrome p450 1B1 : DETOXIFICATION
Location: Chromosome 2 **L432V** **Your Genotype:**	Cytochrome P450 1B1 (CYP1B1) is a Phase I detoxification enzyme responsible for the 4-hydroxylation of estrogen as well as the activation of common environmental toxins such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and aflatoxin B1.
N453S **Your Genotype:**	**Health Implications** · Hyper-induction of CYP1B1 upon exposure to its substrates or inducers · Increased production of 4-hydroxyestrogens and potentially carcinogenic compounds · Possible increased risk of breast cancer, especially in women smokers, those exposed to waste incinerator or agricultural pollutants, and women on HT for 4 years or longer (studies are mixed) · Possible increased risk of cancer of the ovary, uterus, prostate, or lung (studies are mixed) · CYP1B1 polymorphisms are generally associated with higher potential for altered hormone levels and greater menopausal symptoms **Clinical Management Considerations** · Minimize exposure to xenobiotics (e.g., PAHs) and xenoestrogens (e.g., organochlorines), which increase CYP1B1 activity · Maintain a diet rich in antioxidants (colorful fruits and vegetables); consider supplementation · Consider redirecting estrogen metabolism away from 4-hydroxylation using cruciferous vegetables and/or agents such as indole 3-carbinol (I3C), diindolylmethane (DIM), fish oils, or rosemary · Caution using long-term estrogen therapy, especially conjugated equine estrogens, which are preferentially 4-hydroxylated; combined estrogen/progestin therapy produces greatest breast density in carriers of the SNP · Carcinogen-induced DNA damage may be minimized by agents such as curcumin, black cohosh, genistein, and DHEA

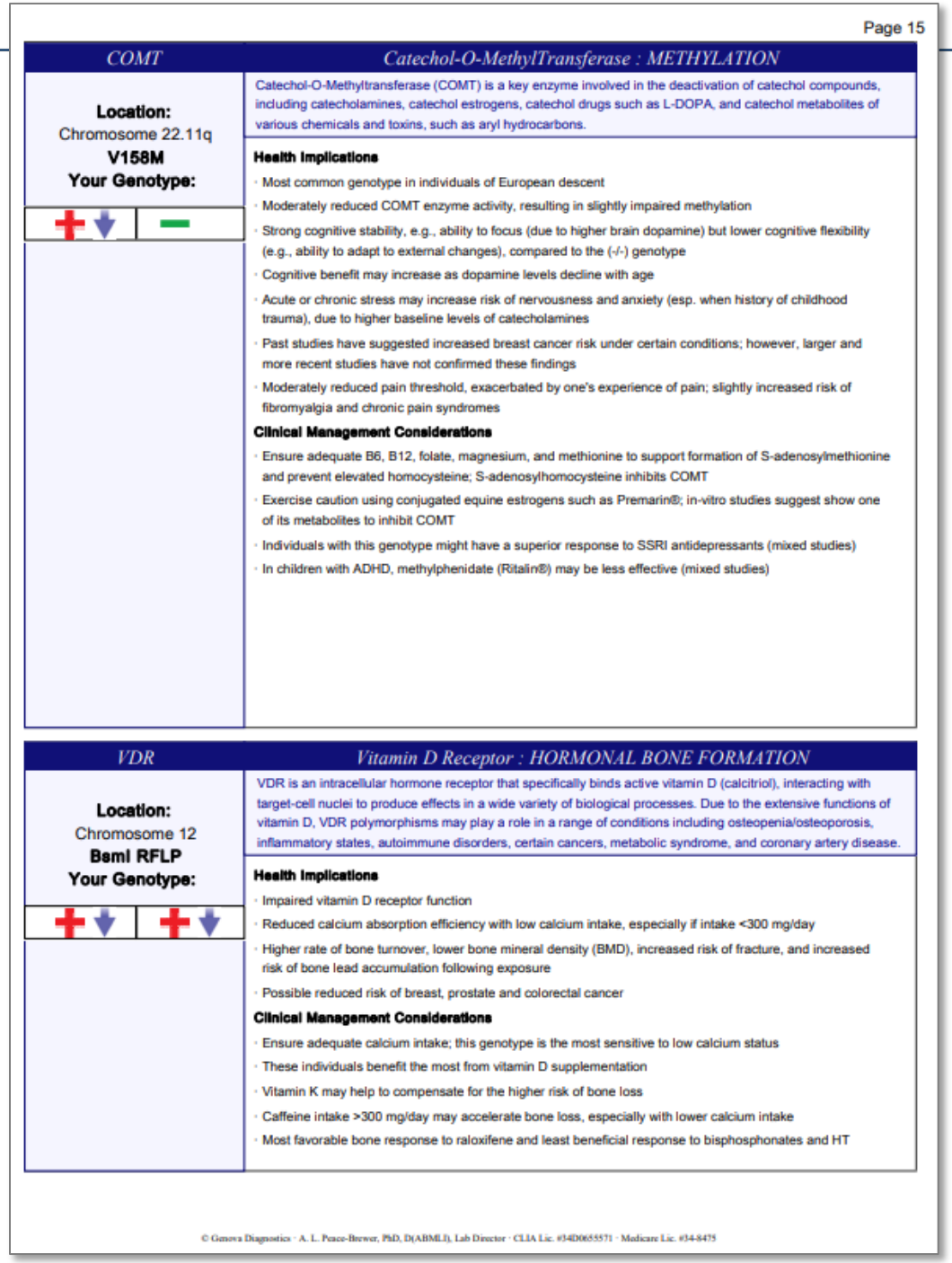
Key
- – – Neither chromosome carries the genetic variation.
+ – One chromosome (of two) carries the genetic variation.
+ + Both chromosomes carry the genetic variation.
(You inherit one chromosome from each parent)

+ ↑ Gene activity increased
+ ↓ Gene activity decreased

GENOVA DIAGNOSTICS

GENOVA DIAGNOSTICS

Case #2:
43 y/o female



COMT — Catechol-O-MethylTransferase : METHYLATION

Location:
Chromosome 22.11q
V158M
Your Genotype:

Catechol-O-Methyltransferase (COMT) is a key enzyme involved in the deactivation of catechol compounds, including catecholamines, catechol estrogens, catechol drugs such as L-DOPA, and catechol metabolites of various chemicals and toxins, such as aryl hydrocarbons.

Health Implications

- Most common genotype in individuals of European descent
- Moderately reduced COMT enzyme activity, resulting in slightly impaired methylation
- Strong cognitive stability, e.g., ability to focus (due to higher brain dopamine) but lower cognitive flexibility (e.g., ability to adapt to external changes), compared to the (-/-) genotype
- Cognitive benefit may increase as dopamine levels decline with age
- Acute or chronic stress may increase risk of nervousness and anxiety (esp. when history of childhood trauma), due to higher baseline levels of catecholamines
- Past studies have suggested increased breast cancer risk under certain conditions; however, larger and more recent studies have not confirmed these findings
- Moderately reduced pain threshold, exacerbated by one's experience of pain; slightly increased risk of fibromyalgia and chronic pain syndromes

Clinical Management Considerations

- Ensure adequate B6, B12, folate, magnesium, and methionine to support formation of S-adenosylmethionine and prevent elevated homocysteine; S-adenosylhomocysteine inhibits COMT
- Exercise caution using conjugated equine estrogens such as Premarin®; in-vitro studies suggest show one of its metabolites to inhibit COMT
- Individuals with this genotype might have a superior response to SSRI antidepressants (mixed studies)
- In children with ADHD, methylphenidate (Ritalin®) may be less effective (mixed studies)

VDR — Vitamin D Receptor : HORMONAL BONE FORMATION

Location:
Chromosome 12
BsmI RFLP
Your Genotype:

VDR is an intracellular hormone receptor that specifically binds active vitamin D (calcitriol), interacting with target-cell nuclei to produce effects in a wide variety of biological processes. Due to the extensive functions of vitamin D, VDR polymorphisms may play a role in a range of conditions including osteopenia/osteoporosis, inflammatory states, autoimmune disorders, certain cancers, metabolic syndrome, and coronary artery disease.

Health Implications

- Impaired vitamin D receptor function
- Reduced calcium absorption efficiency with low calcium intake, especially if intake <300 mg/day
- Higher rate of bone turnover, lower bone mineral density (BMD), increased risk of fracture, and increased risk of bone lead accumulation following exposure
- Possible reduced risk of breast, prostate and colorectal cancer

Clinical Management Considerations

- Ensure adequate calcium intake; this genotype is the most sensitive to low calcium status
- These individuals benefit the most from vitamin D supplementation
- Vitamin K may help to compensate for the higher risk of bone loss
- Caffeine intake >300 mg/day may accelerate bone loss, especially with lower calcium intake
- Most favorable bone response to raloxifene and least beneficial response to bisphosphonates and HT

GENOVA DIAGNOSTICS

Case #2 (Cont.)

- Her vitamin D level was 29 which is not surprising considering her genetic test.
- Start D3 3,000 IU daily.
- Since the patient has + thyroid antibodies. Do a GI effects test.
- After fixing her gut, start the patient on LDN.
- Stress reduction techniques.
- Start adaptogenic herbs: rhodiola, ginseng, Ashwagandha.
- Order an U/S of the thyroid to see if the patient has thyroiditis.

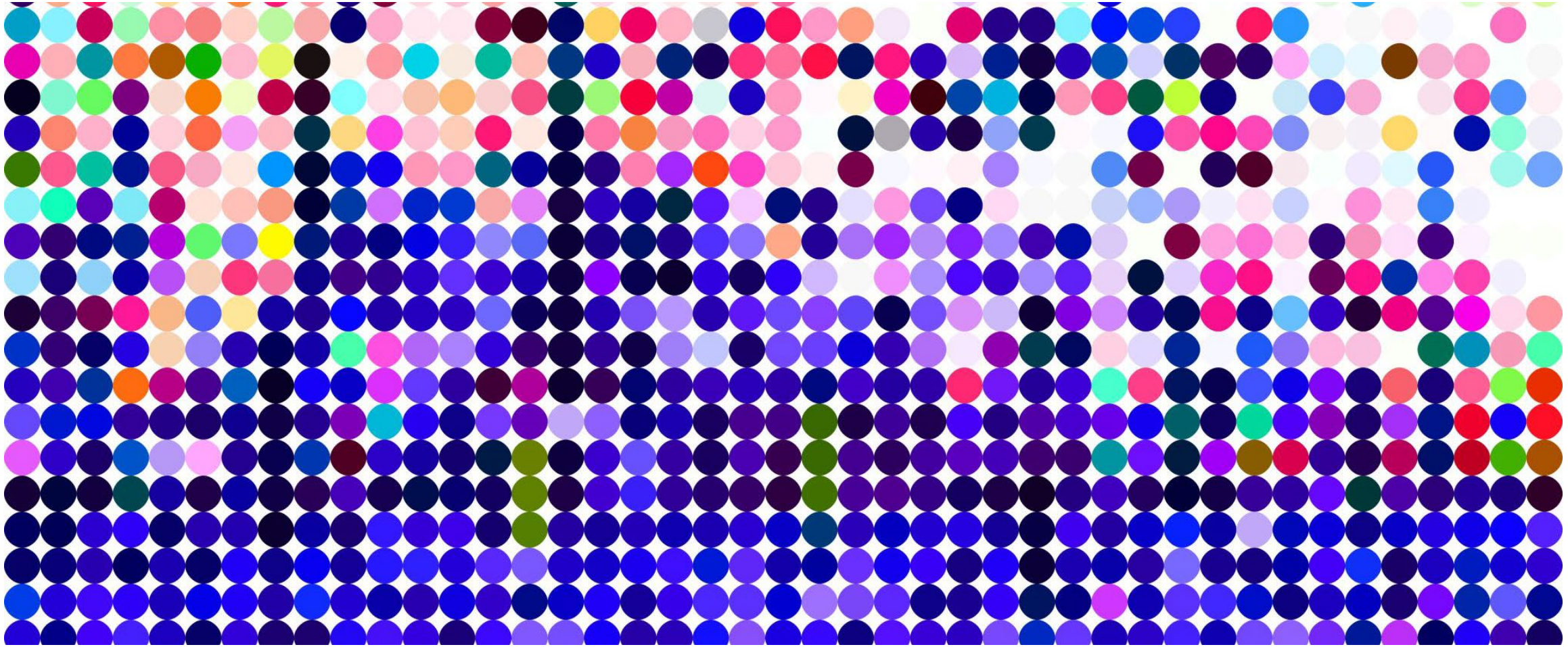
Case #2 (Cont.)

- Reverse T3 is upper limit of normal. COVID long-haul is an autoimmune mitochondrial illness. Start the following nutrients:
  - Magnesium glycinate: 400 mg daily
  - Coenzyme Q-10: 300 mg daily
  - Alpha lipoic acid: 300 mg daily
  - Measure TMAO levels. If normal: Start L-carnitine 2,000 mg daily if the patient has normal renal function
  - D-ribose: 15 grams (5 grams three times a day)
  - Nitric oxide: two daily

Case #3: 58 y/o female

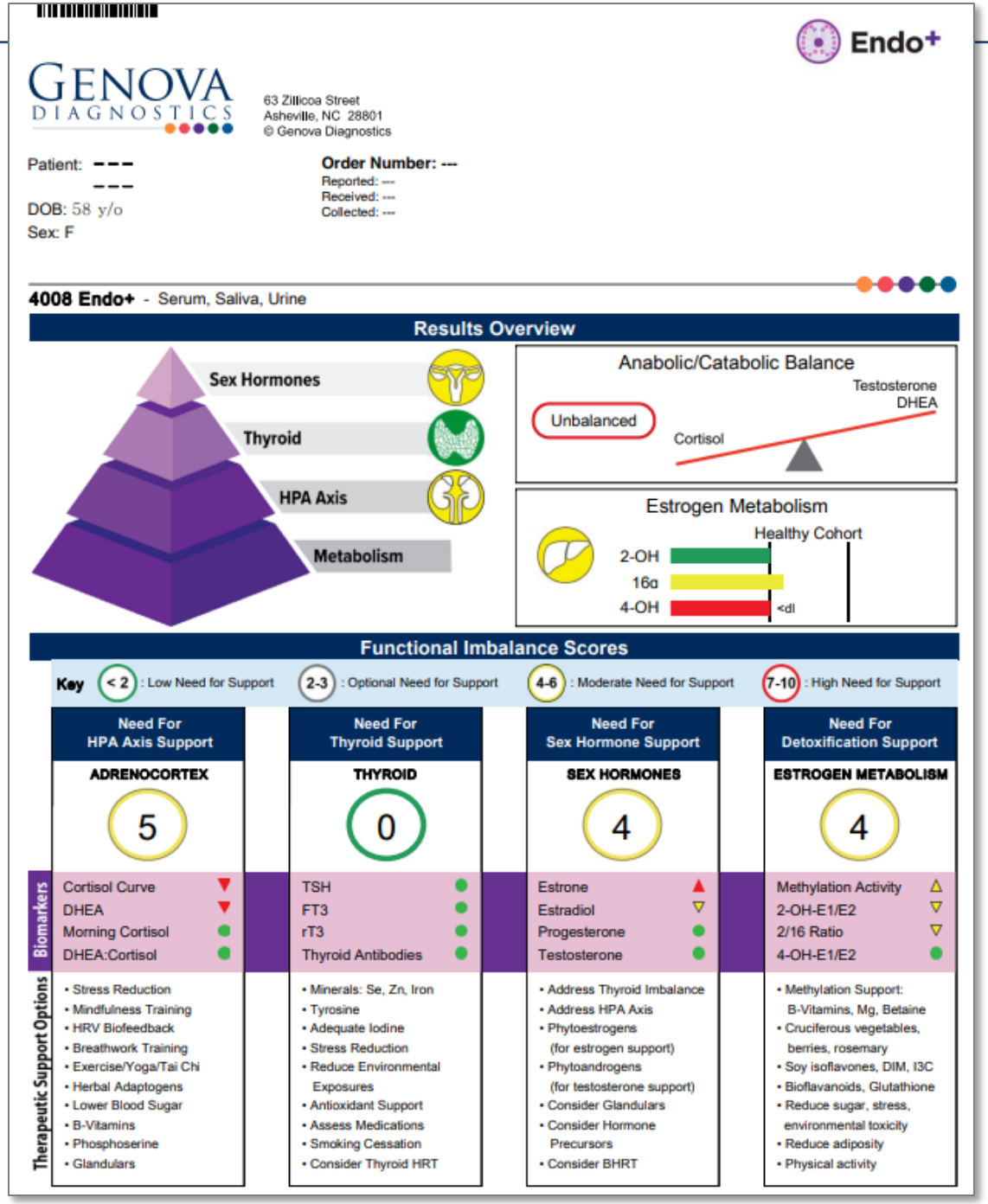
- This is a 58-year-old female who presents to the office with the chief complaint that she does not feel well. She has gained 30 pounds since starting hormones.
- PH: S/P tonsillectomy, S/P right shoulder surgery
- SH: patient is a nurse practitioner
- FH: mother has CAD and cataracts. Father died three years ago from COVID related symptoms. She has one sister who she is estranged from.
- Meds: progesterone 225 mg qhs
- Vitamins: MVI, calcium, magnesium, probiotic, EPA/DHA 2,000 mg, vitamin D 5,000 IU, lipoic acid 100 mg, coenzyme Q-10 100 mg
- ROS: + anxiety, mood swings, incontinence, fatigue, breast swelling, and tenderness

What Do You Want To Do With This Patient?



GENOVA DIAGNOSTICS

Case #3:
58 y/o female



GENOVA DIAGNOSTICS
63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Endo+

Patient: ---

DOB: 58 y/o
Sex: F

Order Number: ---
Reported: ---
Received: ---
Collected: ---

4008 Endo+ - Serum, Saliva, Urine

Results Overview

Sex Hormones
Thyroid
HPA Axis
Metabolism

Anabolic/Catabolic Balance
Unbalanced
Testosterone
DHEA
Cortisol

Estrogen Metabolism
Healthy Cohort
2-OH
16α
4-OH
<dl

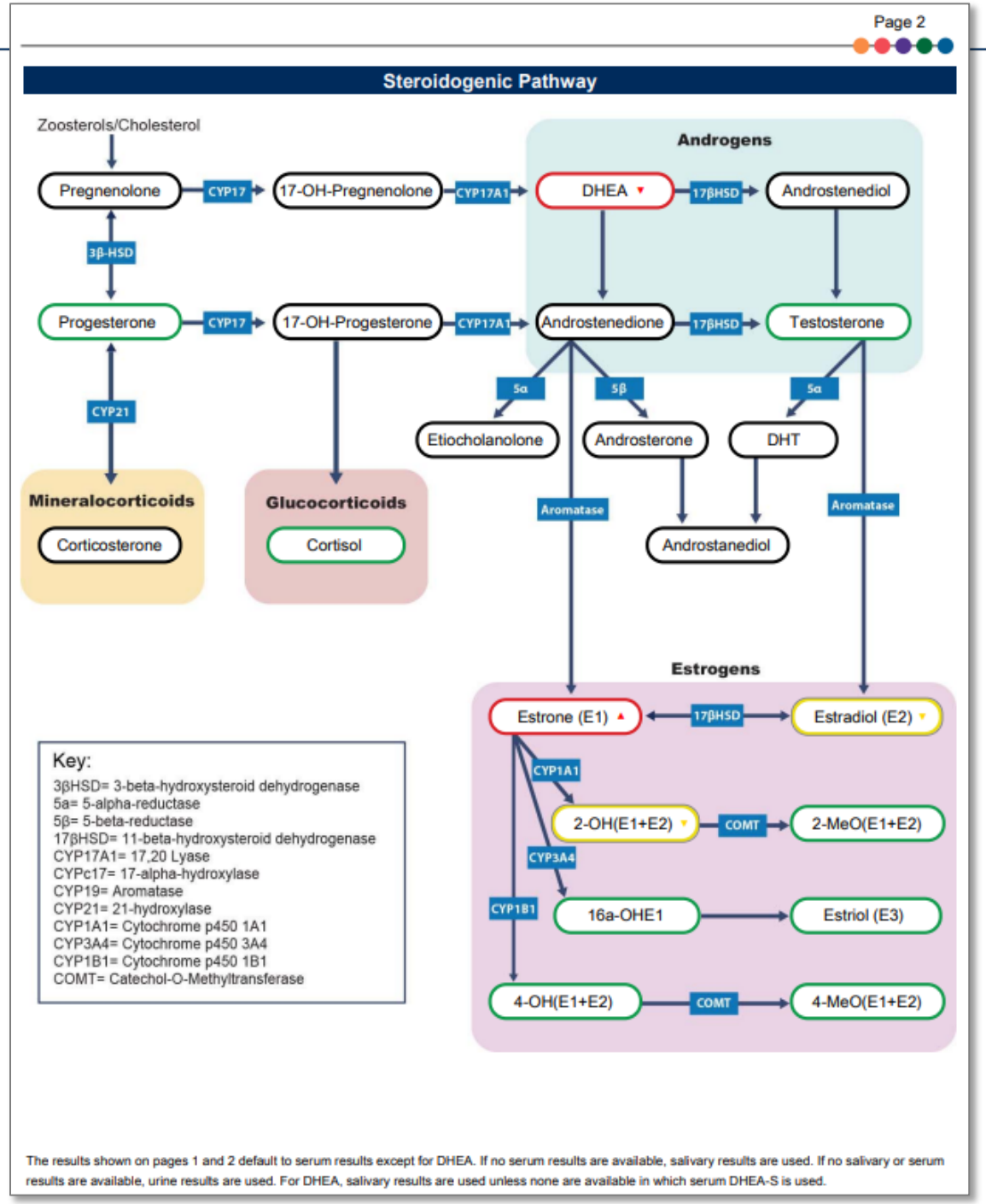
Functional Imbalance Scores

Key: < 2 : Low Need for Support; 2-3 : Optional Need for Support; 4-6 : Moderate Need for Support; 7-10 : High Need for Support

	Need For HPA Axis Support	Need For Thyroid Support	Need For Sex Hormone Support	Need For Detoxification Support
	ADRENOCORTEX	THYROID	SEX HORMONES	ESTROGEN METABOLISM
	5	0	4	4
Biomarkers	Cortisol Curve ▼ DHEA ▼ Morning Cortisol ● DHEA:Cortisol ●	TSH ● FT3 ● rT3 ● Thyroid Antibodies ●	Estrone ▲ Estradiol ▽ Progesterone ● Testosterone ●	Methylation Activity △ 2-OH-E1/E2 ▽ 2/16 Ratio ▽ 4-OH-E1/E2 ●
Therapeutic Support Options	• Stress Reduction • Mindfulness Training • HRV Biofeedback • Breathwork Training • Exercise/Yoga/Tai Chi • Herbal Adaptogens • Lower Blood Sugar • B-Vitamins • Phosphoserine • Glandulars	• Minerals: Se, Zn, Iron • Tyrosine • Adequate Iodine • Stress Reduction • Reduce Environmental Exposures • Antioxidant Support • Assess Medications • Smoking Cessation • Consider Thyroid HRT	• Address Thyroid Imbalance • Address HPA Axis • Phytoestrogens (for estrogen support) • Phytoandrogens (for testosterone support) • Consider Glandulars • Consider Hormone Precursors • Consider BHRT	• Methylation Support: B-Vitamins, Mg, Betaine • Cruciferous vegetables, berries, rosemary • Soy isoflavones, DIM, I3C • Bioflavanoids, Glutathione • Reduce sugar, stress, environmental toxicity • Reduce adiposity • Physical activity

GENOVA DIAGNOSTICS

Case #3:
58 y/o female



GENOVA DIAGNOSTICS

Case #3:
58 y/o female

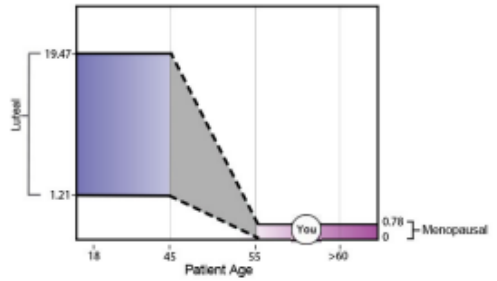
Endo+ Serum

Methodology: Chemiluminescent, RIA

Serum Sex Hormones

Progesterone

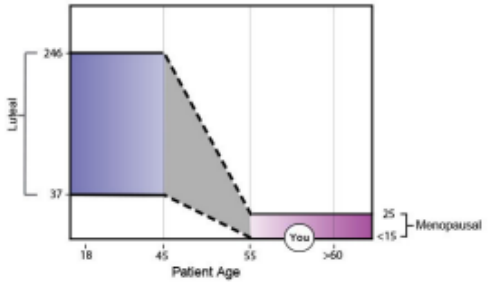
Progesterone



		Reference Range
Progesterone	0.49	See Chart Below

Estrogens

Estradiol (E2)



		Reference Range
Estradiol (E2)	<15	See Chart Below
Estrone (E1)	93	18-63 pg/mL
Estriol (E3)	<80	<= 80 pg/mL

Androgens

DHEA-S	70	8-188 mcg/dL
Testosterone, Total	0.34	<0.10-0.75 ng/mL
Free Androgen Index	0.96	0.32-6.73

Binding Proteins

Sex Hormone Binding Globulin	123.3	16.8-125.2 nmol/L

Reference Range Information

Serum Analyte	Premenopause Luteal	Unsupplemented Menopause	Unsupplemented Male	Patient Result
Estrone (pg/mL)	43 - 250	18 - 63	46 - 143	93
Estradiol (pg/mL)	37 - 246	<15 - 25	<15 - 32	<15
Estriol (pg/mL)	<=80	<=80	<=80	<80
Progesterone (ng/mL)	1.21 - 19.47	<=0.78	<=2.06	0.49
Testosterone (ng/mL)	<0.10 - 0.75	<0.10 - 0.75	1.75 - 7.81	0.34
Sex Hormone Binding Globulin (nmol/L)	18.2 - 135.5	16.8 - 125.2	13.3 - 89.5	123.3
Free Androgen Index	0.43 - 8.48	0.32 - 6.73	N/A	0.96

These reference ranges are based on menopausal patients. If patient is premenopausal, refer to the chart above to determine the appropriate clinical ranges.
Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.
The testosterone reference range is based on the manufacturer's range determined from women ages 21-73.

GENOVA DIAGNOSTICS

Case #3:
58 y/o female

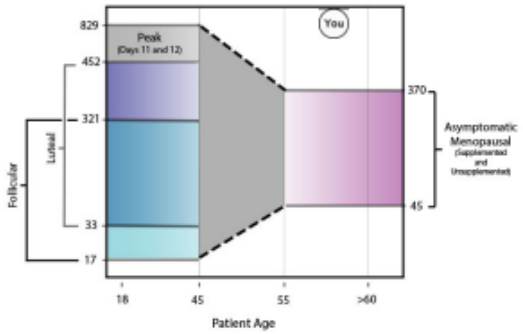
Endo+ Saliva

Methodology: EIA, LIA

Salivary Sex Hormones

Progesterone

Progesterone



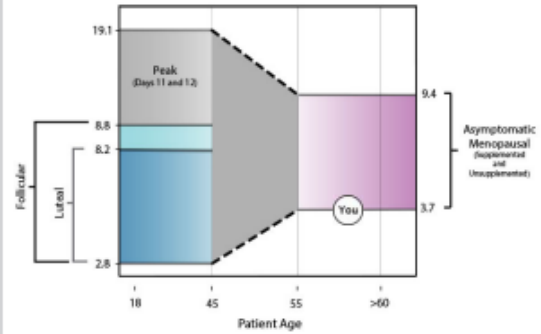
		Reference Range
Progesterone	856	See Chart Below

Androgens

DHEA ◆	60	71-640 pg/mL
Testosterone	<30	34-148 pmol/L

Estrogens

Estradiol (E2)



		Reference Range
Estradiol (E2)	3.7	See Chart Below
Estrone (E1) * ◆	69.6	31.9-183.4 pmol/L
Estriol (E3) * ◆	<70	<= 133 pmol/L

**Reference ranges for Estrone and Estriol are based on menopausal patients.*

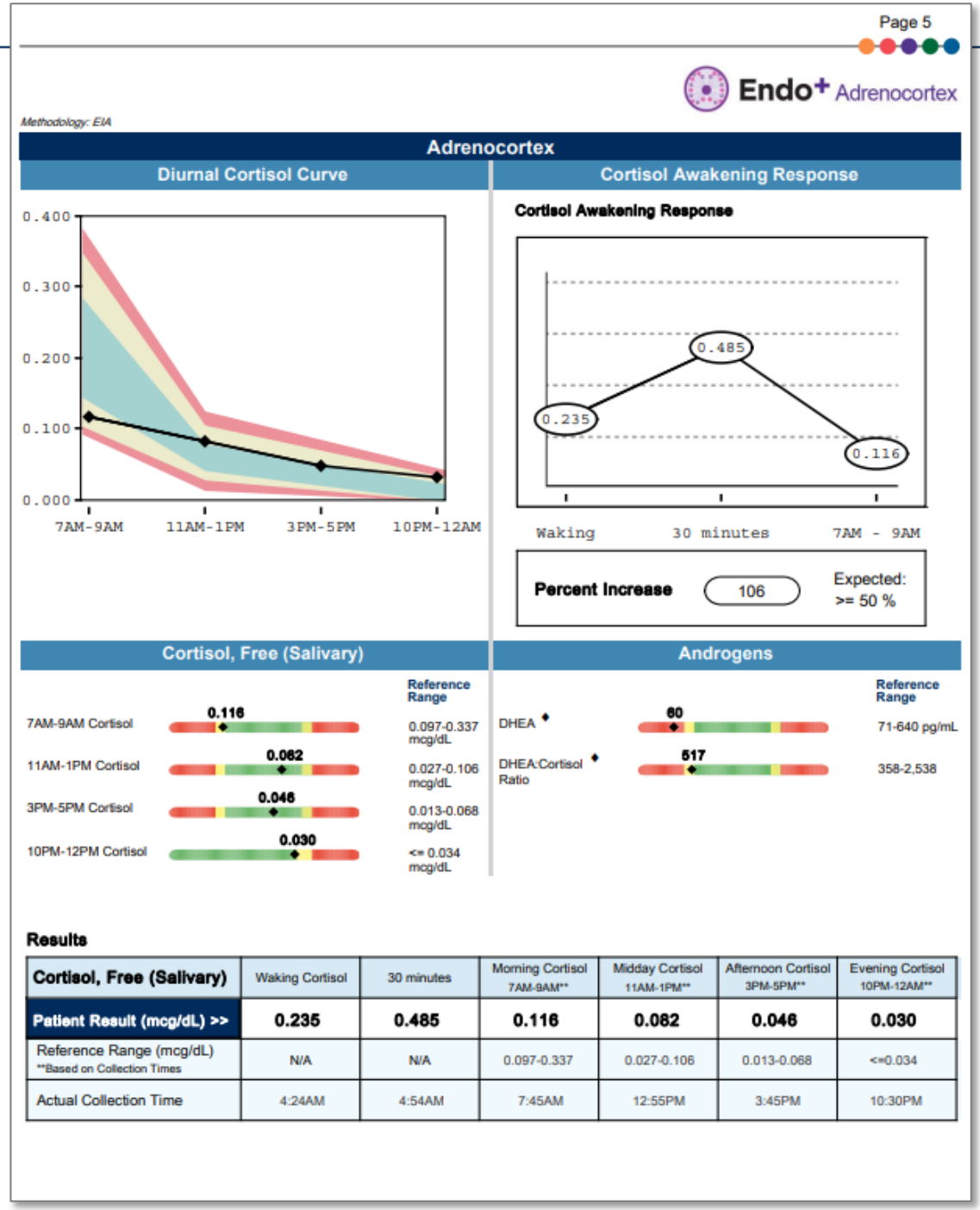
Reference Range Information

Saliva Analyte	Luteal	Follicular	Menopausal	Male	Patient Result
Estrone (pmol/L)	N/A	N/A	31.9 - 183.4	N/A	69.6
Estradiol (pmol/L)	2.8 - 8.2	2.8 - 8.8	3.7 - 9.4	3.1 - 7.4	3.7
Estriol (pmol/L)	N/A	N/A	<=133	N/A	<70
Progesterone (pmol/L)	33 - 452	17 - 321	45 - 370	31 - 280	856
Testosterone (pmol/L)	34 - 148	34 - 148	34 - 148	110 - 513	<30
DHEA (pg/mL)	71 - 640	71 - 640	71 - 640	71 - 640	60

These reference ranges are based on menopausal patients. If patient is premenopausal, refer to the chart above to determine the appropriate clinical ranges.
Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

GENOVA DIAGNOSTICS

Case #3:
58 y/o female



Endo+ Adrenocortex

Methodology: EIA

Adrenocortex

Diurnal Cortisol Curve

Cortisol Awakening Response

Cortisol Awakening Response

Percent Increase 106 Expected: >= 50 %

Cortisol, Free (Salivary)

		Reference Range
7AM-9AM Cortisol	0.116	0.097-0.337 mcg/dL
11AM-1PM Cortisol	0.082	0.027-0.106 mcg/dL
3PM-5PM Cortisol	0.046	0.013-0.068 mcg/dL
10PM-12PM Cortisol	0.030	<= 0.034 mcg/dL

Androgens

		Reference Range
DHEA	60	71-640 pg/mL
DHEA:Cortisol Ratio	517	358-2,538

Results

Cortisol, Free (Salivary)	Waking Cortisol	30 minutes	Morning Cortisol 7AM-9AM**	Midday Cortisol 11AM-1PM**	Afternoon Cortisol 3PM-5PM**	Evening Cortisol 10PM-12AM**
Patient Result (mcg/dL) >>	**0.235**	**0.485**	**0.116**	**0.082**	**0.046**	**0.030**
Reference Range (mcg/dL) **Based on Collection Times	N/A	N/A	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
Actual Collection Time	4:24AM	4:54AM	7:45AM	12:55PM	3:45PM	10:30PM

GENOVA DIAGNOSTICS

Case #3:
58 y/o female

Endo+ Urine

Methodology: LC/MS/MS

Estrogen Metabolism

Urine Estrogens

		Reference Range
Estrone (E1)	0.7	1.1-26.2 mcg/g Creat.
Estradiol (E2)	<dl	0.6-15.4 mcg/g Creat.
Estriol (E3)	2.2	0.7-30.8 mcg/g Creat.

Phase 1 Estrogen Metabolites

		Reference Range
2-Hydroxyestrone+ 2-Hydroxyestradiol (2-OH(E1+E2))	1.0	0.9-43.8 mcg/g Creat.
16α-Hydroxyestrone (16α-OHE1)	1.6	0.4-7.7 mcg/g Creat.
4-Hydroxyestrone+ 4-Hydroxyestradiol (4-OH(E1+E2))	<dl	<= 8.8 mcg/g Creat.

Enzyme Activity

2-OH(E1+E2)/ 16α-OHE1 Ratio	0.6	0.3-15.1
Methylation Activity (2-OH/2-MeO Ratio)	0.9	0.4-11.6

Poorer Methylation

Phase 2 Estrogen Metabolites

2-Methoxyestrone+ 2-Methoxyestradiol (2-MeO(E1+E2))	1.1	0.3-5.9 mcg/g Creat.
4-Methoxyestrone+ 4-Methoxyestradiol (4-MeO(E1+E2))	<dl	<= 1.0 mcg/g Creat.

Reference Range Information

Urine Analyte	Premenopause Luteal	Menopause	Male	Patient Result
Estrone (mcg/g Creat.)	2 - 26.2	1.1 - 26.2	1.6 - 8.6	0.7
Estradiol (mcg/g Creat.)	0.6 - 11.2	0.6 - 15.4	0.8 - 4.3	<dl
Estriol (mcg/g Creat.)	0.6 - 19.9	0.7 - 30.8	0.3 - 5.1	2.2
2-OH(E1+E2) (mcg/g Creat.)	1.3 - 36.3	0.9 - 43.8	0.7 - 12.5	1.0
16a-OHE1 (mcg/g Creat.)	0.5 - 8.9	0.4 - 7.7	<=2.0	1.6
4-OH(E1+E2) (mcg/g Creat.)	<=5.9	<=8.8	<=1.6	<dl
2-MeO(E1+E2) (mcg/g Creat.)	0.2 - 8.6	0.3 - 5.9	0.2 - 2.5	1.1
4-MeO(E1+E2) (mcg/g Creat.)	<=1.0	<=1.0	<=1.0	<dl
2-OH(E1+E2)/16a-OHE1 Ratio	0.3 - 13.7	0.3 - 15.1	0.8 - 12.9	0.6
2-OH/2-MeO Ratio	1.6 - 10.7	0.4 - 11.6	1.0 - 8.8	0.9

These reference ranges are based on menopausal patients. If patient is premenopausal, refer to the chart above to determine the appropriate clinical ranges.
Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

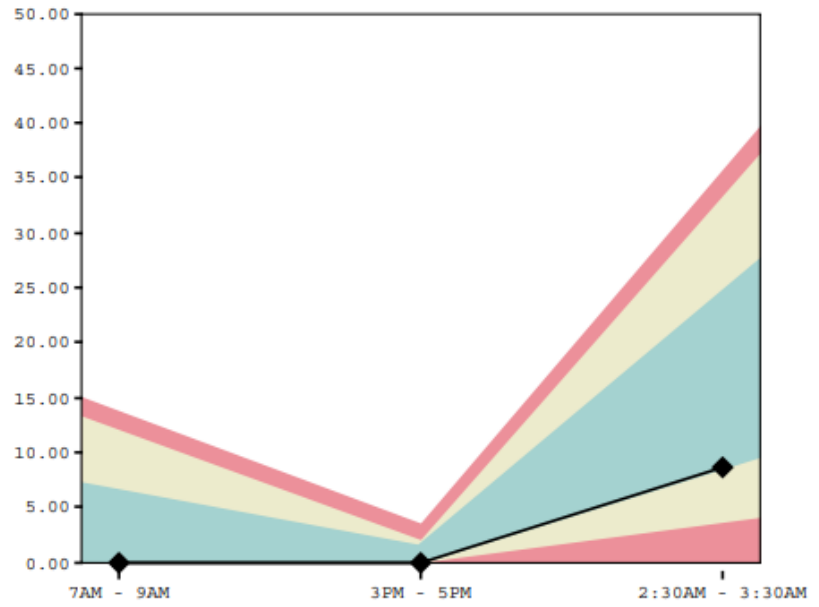
GENOVA DIAGNOSTICS

Case #3:
58 y/o female

Endo+ Melatonin

Methodology: EIA

Salivary Melatonin

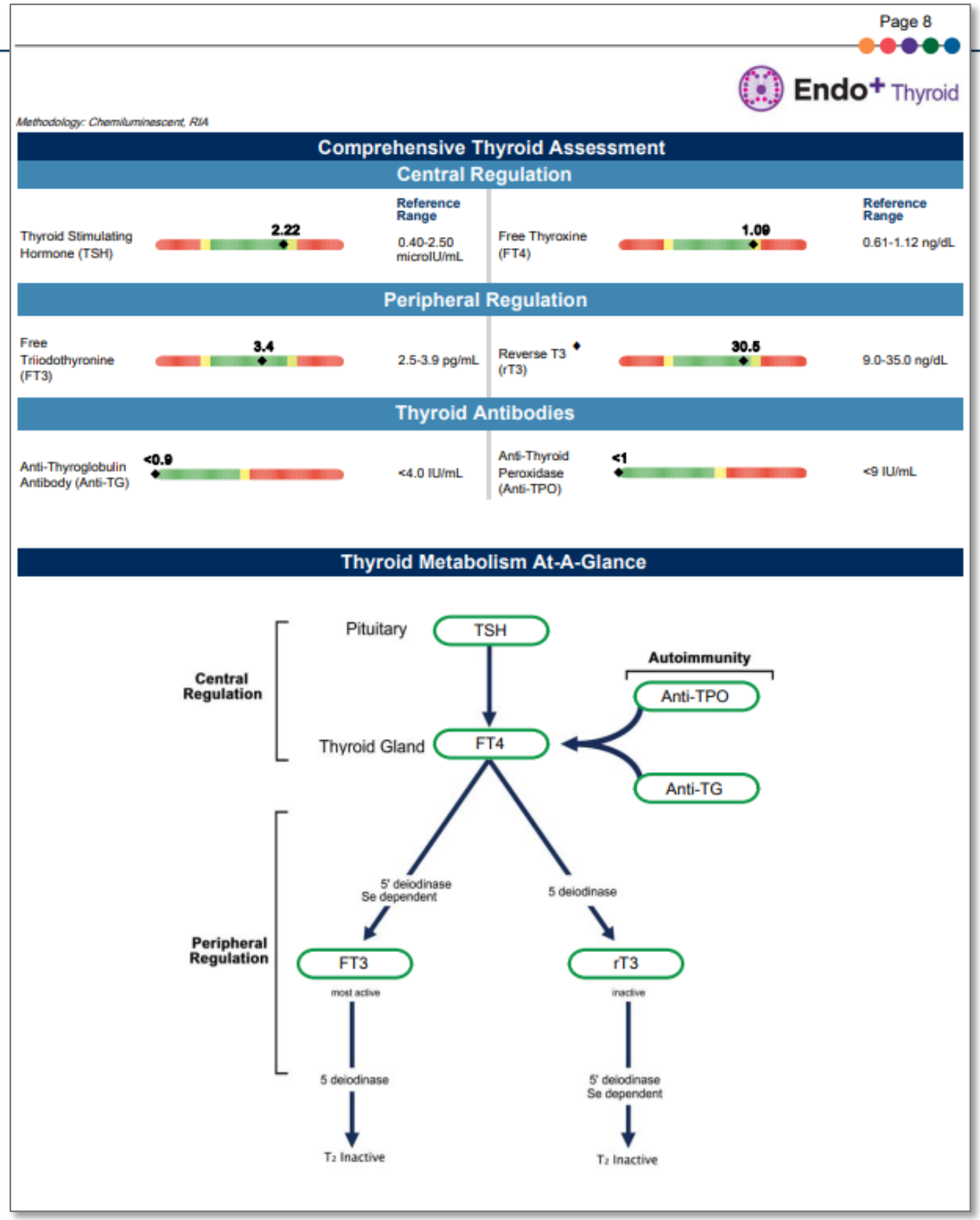


Results

Salivary Melatonin ♦	7AM-9AM**	3PM-5PM**	2:30AM-3:30AM**
Patient Result (pg/mL) >>	**<1.56**	**<1.56**	**8.55**
Reference Range (pg/mL) **Based on Collection Times	<=12.12	<=1.97	3.71-33.38

GENOVA DIAGNOSTICS

Case #3:
58 y/o female



Endo+ Thyroid

Methodology: Chemiluminescent, RIA

Comprehensive Thyroid Assessment

Central Regulation

		Reference Range			Reference Range
Thyroid Stimulating Hormone (TSH)	2.22	0.40-2.50 microIU/mL	Free Thyroxine (FT4)	1.09	0.61-1.12 ng/dL

Peripheral Regulation

Free Triiodothyronine (FT3)	3.4	2.5-3.9 pg/mL	Reverse T3 (rT3)	30.5	9.0-35.0 ng/dL

Thyroid Antibodies

Anti-Thyroglobulin Antibody (Anti-TG)	<0.9	<4.0 IU/mL	Anti-Thyroid Peroxidase (Anti-TPO)	<1	<9 IU/mL

Thyroid Metabolism At-A-Glance

GENOVA DIAGNOSTICS

Case #3:
58 y/o female

Additional Tests

Analyte		Reference Range
Secretory IgA (saliva) ♦	88	56-212 mcg/mL
Prolactin (serum) *	9.87	2.74-19.64 ng/mL
Androstenedione (serum) * † ♦	48	41-262 ng/dL
Luteinizing Hormone (serum) *	62.5	7.7-58.5 mIU/mL
Follicle Stimulating Hormone (serum) *	170.0	25.8-134.8 mIU/mL

* Please see commentary section for relevant testing location and reference range details.

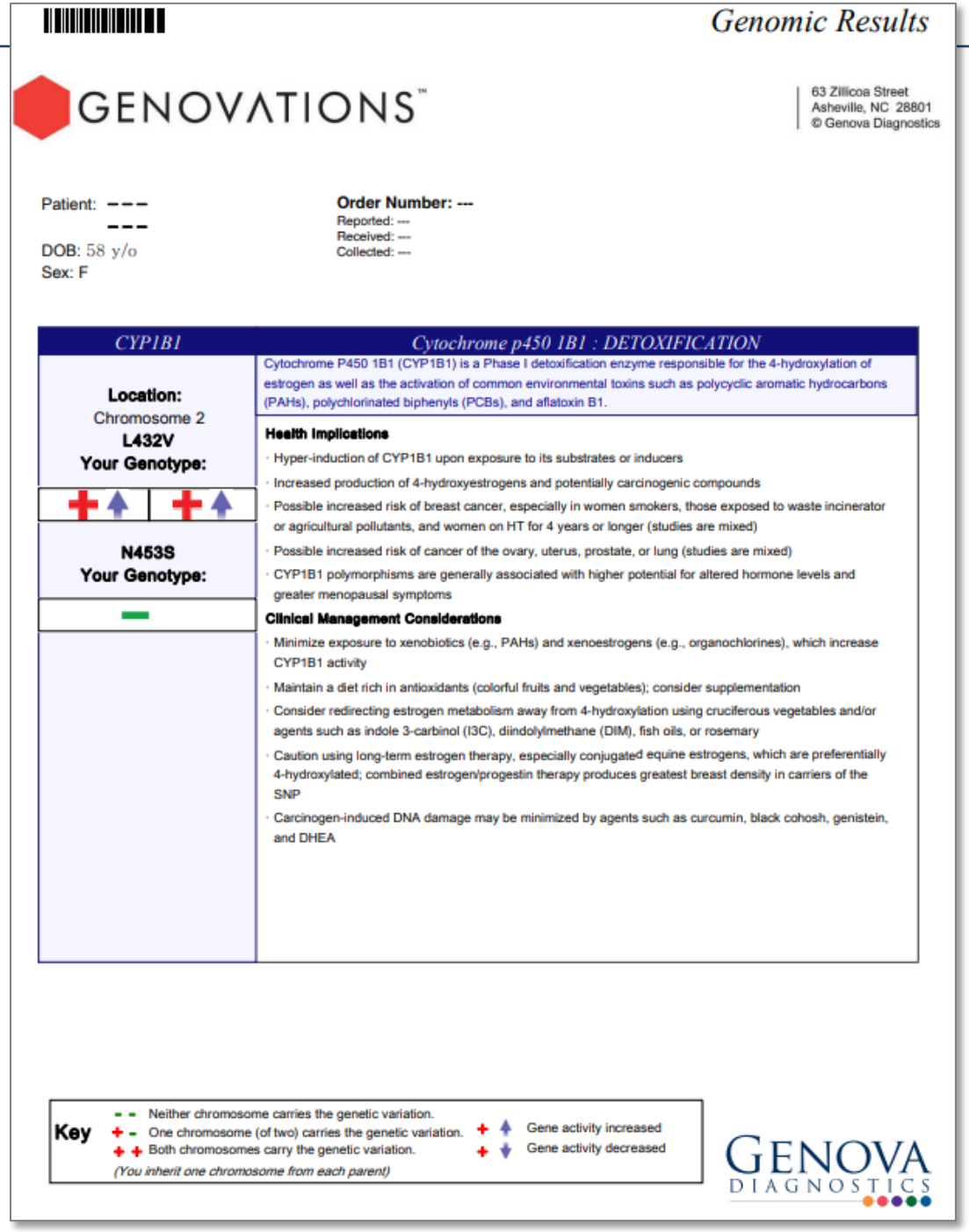
† Reference ranges are age dependent.

Analyte	Premenopause Luteal	Unsupplemented Menopause	Male	Patient Results
Prolactin (ng/mL)	3.34 - 26.72	2.74 - 19.64	2.64 - 13.13	9.87
Luteinizing Hormone (mIU/mL)	1.0 - 11.4	7.7 - 58.5	1.7 - 8.6	62.5
FSH (mIU/mL)	1.7 - 7.7	25.8 - 134.8	1.5 - 12.4	170.0

These reference ranges are based on menopausal patients. If patient is premenopausal, refer to the chart below to determine the appropriate clinical ranges. Each individual is unique and evaluation of hormone status should be within the context of the patient's clinical picture.

GENOVA DIAGNOSTICS

Case #3:
58 y/o female



Genomic Results

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Patient: ---

DOB: 58 y/o
Sex: F

Order Number: ---
Reported: ---
Received: ---
Collected: ---

CYP1B1	Cytochrome p450 1B1 : DETOXIFICATION
Location: Chromosome 2 **L432V Your Genotype:**	Cytochrome P450 1B1 (CYP1B1) is a Phase I detoxification enzyme responsible for the 4-hydroxylation of estrogen as well as the activation of common environmental toxins such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and aflatoxin B1.
✚▲ ✚▲	**Health Implications** · Hyper-induction of CYP1B1 upon exposure to its substrates or inducers · Increased production of 4-hydroxyestrogens and potentially carcinogenic compounds · Possible increased risk of breast cancer, especially in women smokers, those exposed to waste incinerator or agricultural pollutants, and women on HT for 4 years or longer (studies are mixed) · Possible increased risk of cancer of the ovary, uterus, prostate, or lung (studies are mixed) · CYP1B1 polymorphisms are generally associated with higher potential for altered hormone levels and greater menopausal symptoms
N453S Your Genotype:	**Clinical Management Considerations** · Minimize exposure to xenobiotics (e.g., PAHs) and xenoestrogens (e.g., organochlorines), which increase CYP1B1 activity · Maintain a diet rich in antioxidants (colorful fruits and vegetables); consider supplementation · Consider redirecting estrogen metabolism away from 4-hydroxylation using cruciferous vegetables and/or agents such as indole 3-carbinol (I3C), diindolylmethane (DIM), fish oils, or rosemary · Caution using long-term estrogen therapy, especially conjugated equine estrogens, which are preferentially 4-hydroxylated; combined estrogen/progestin therapy produces greatest breast density in carriers of the SNP · Carcinogen-induced DNA damage may be minimized by agents such as curcumin, black cohosh, genistein, and DHEA
▬	

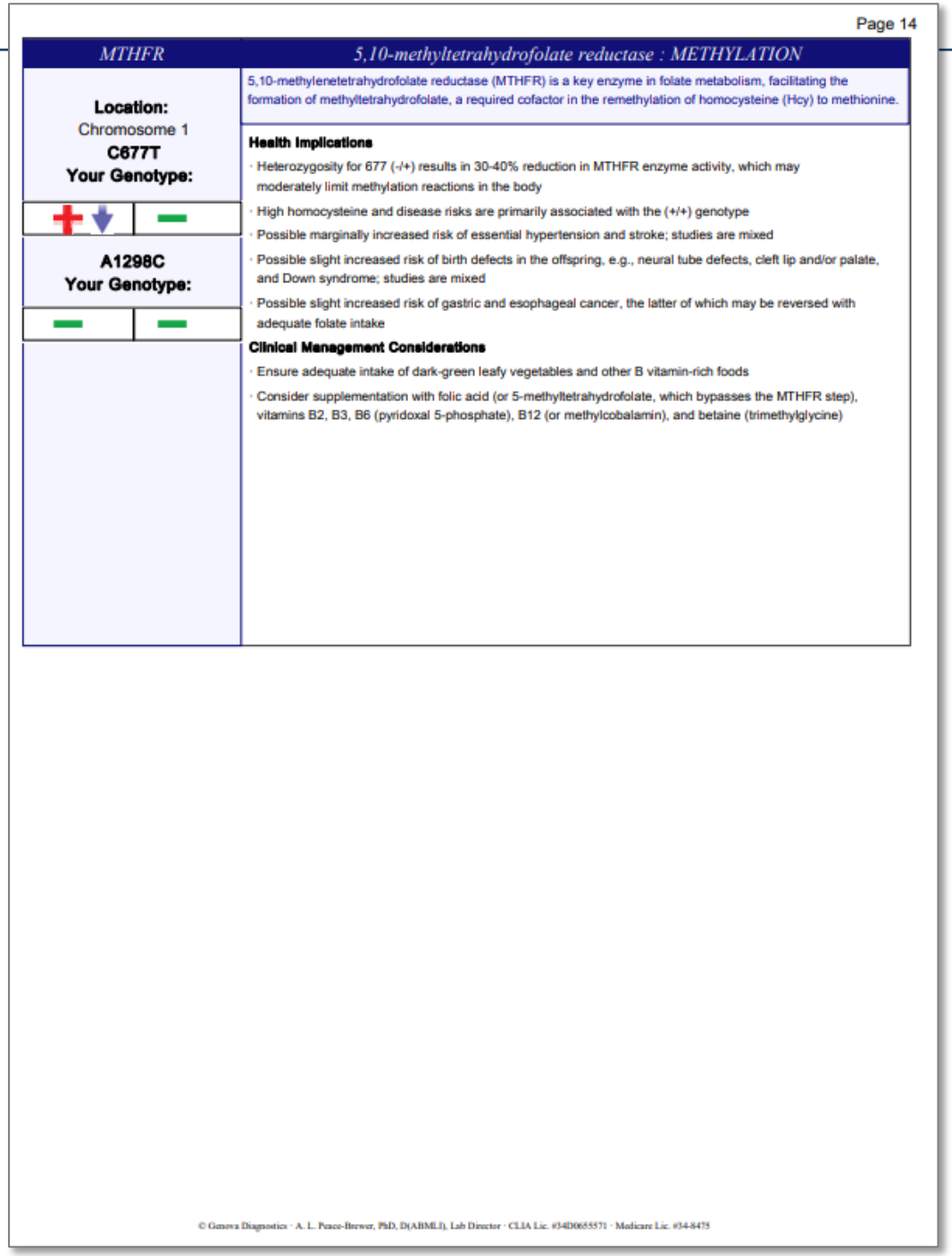
Key
- - Neither chromosome carries the genetic variation.
✚ - One chromosome (of two) carries the genetic variation.
✚ ✚ Both chromosomes carry the genetic variation.
(You inherit one chromosome from each parent)

✚▲ Gene activity increased
✚▼ Gene activity decreased

GENOVA DIAGNOSTICS

GENOVA DIAGNOSTICS

Case #3:
58 y/o female

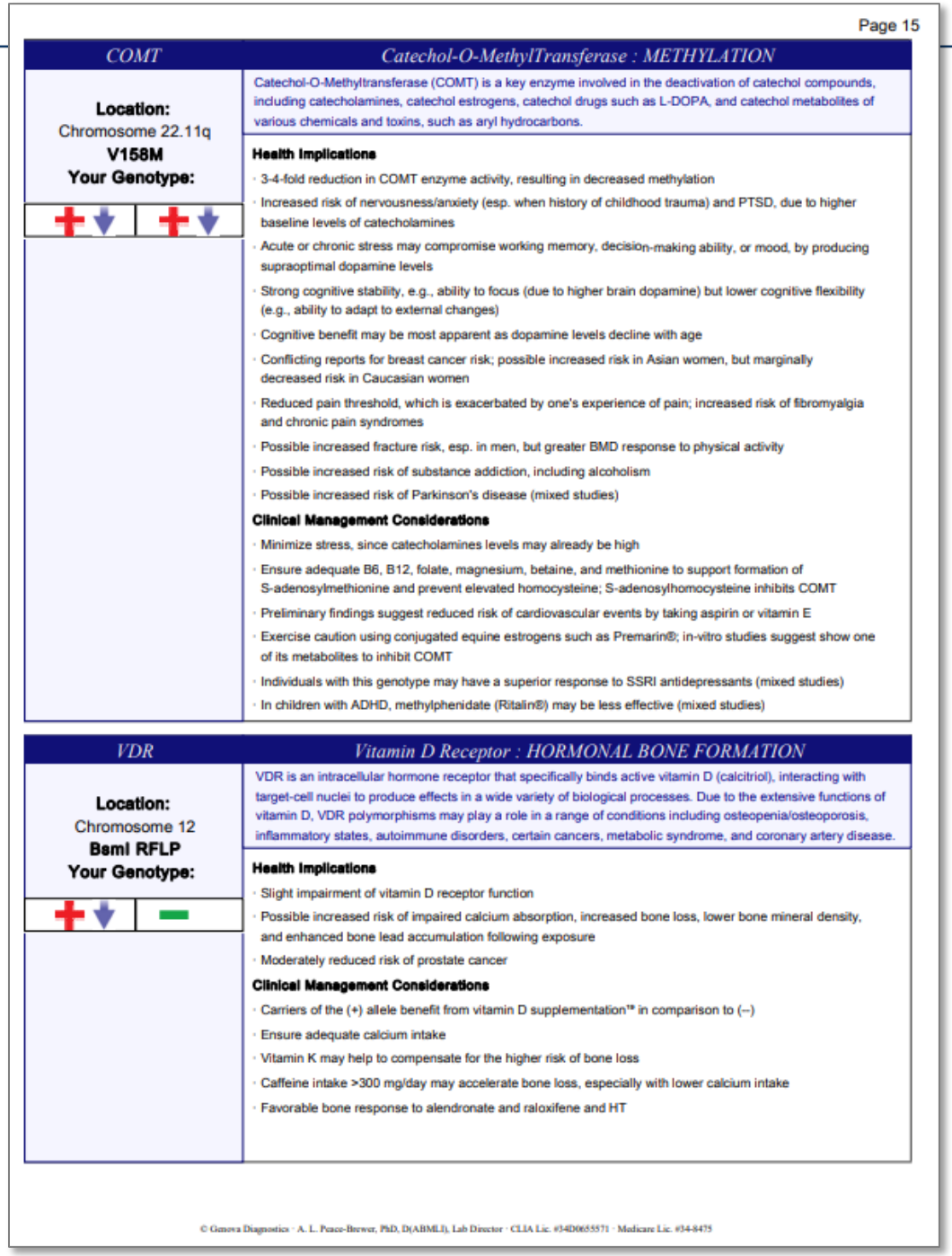


Page 14

MTHFR	5,10-methyltetrahydrofolate reductase : METHYLATION
Location: Chromosome 1 **C677T Your Genotype:**	5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism, facilitating the formation of methyltetrahydrofolate, a required cofactor in the remethylation of homocysteine (Hcy) to methionine.
A1298C Your Genotype:	**Health Implications** · Heterozygosity for 677 (-/+) results in 30-40% reduction in MTHFR enzyme activity, which may moderately limit methylation reactions in the body · High homocysteine and disease risks are primarily associated with the (+/+) genotype · Possible marginally increased risk of essential hypertension and stroke; studies are mixed · Possible slight increased risk of birth defects in the offspring, e.g., neural tube defects, cleft lip and/or palate, and Down syndrome; studies are mixed · Possible slight increased risk of gastric and esophageal cancer, the latter of which may be reversed with adequate folate intake **Clinical Management Considerations** · Ensure adequate intake of dark-green leafy vegetables and other B vitamin-rich foods · Consider supplementation with folic acid (or 5-methyltetrahydrofolate, which bypasses the MTHFR step), vitamins B2, B3, B6 (pyridoxal 5-phosphate), B12 (or methylcobalamin), and betaine (trimethylglycine)

GENOVA DIAGNOSTICS

Case #3:
58 y/o female



COMT — Catechol-O-MethylTransferase : METHYLATION

Location:
Chromosome 22.11q
V158M
Your Genotype:

Catechol-O-Methyltransferase (COMT) is a key enzyme involved in the deactivation of catechol compounds, including catecholamines, catechol estrogens, catechol drugs such as L-DOPA, and catechol metabolites of various chemicals and toxins, such as aryl hydrocarbons.

Health Implications

- 3-4-fold reduction in COMT enzyme activity, resulting in decreased methylation
- Increased risk of nervousness/anxiety (esp. when history of childhood trauma) and PTSD, due to higher baseline levels of catecholamines
- Acute or chronic stress may compromise working memory, decision-making ability, or mood, by producing supraoptimal dopamine levels
- Strong cognitive stability, e.g., ability to focus (due to higher brain dopamine) but lower cognitive flexibility (e.g., ability to adapt to external changes)
- Cognitive benefit may be most apparent as dopamine levels decline with age
- Conflicting reports for breast cancer risk; possible increased risk in Asian women, but marginally decreased risk in Caucasian women
- Reduced pain threshold, which is exacerbated by one's experience of pain; increased risk of fibromyalgia and chronic pain syndromes
- Possible increased fracture risk, esp. in men, but greater BMD response to physical activity
- Possible increased risk of substance addiction, including alcoholism
- Possible increased risk of Parkinson's disease (mixed studies)

Clinical Management Considerations

- Minimize stress, since catecholamines levels may already be high
- Ensure adequate B6, B12, folate, magnesium, betaine, and methionine to support formation of S-adenosylmethionine and prevent elevated homocysteine; S-adenosylhomocysteine inhibits COMT
- Preliminary findings suggest reduced risk of cardiovascular events by taking aspirin or vitamin E
- Exercise caution using conjugated equine estrogens such as Premarin®; in-vitro studies suggest show one of its metabolites to inhibit COMT
- Individuals with this genotype may have a superior response to SSRI antidepressants (mixed studies)
- In children with ADHD, methylphenidate (Ritalin®) may be less effective (mixed studies)

VDR — Vitamin D Receptor : HORMONAL BONE FORMATION

Location:
Chromosome 12
BsmI RFLP
Your Genotype:

VDR is an intracellular hormone receptor that specifically binds active vitamin D (calcitriol), interacting with target-cell nuclei to produce effects in a wide variety of biological processes. Due to the extensive functions of vitamin D, VDR polymorphisms may play a role in a range of conditions including osteopenia/osteoporosis, inflammatory states, autoimmune disorders, certain cancers, metabolic syndrome, and coronary artery disease.

Health Implications

- Slight impairment of vitamin D receptor function
- Possible increased risk of impaired calcium absorption, increased bone loss, lower bone mineral density, and enhanced bone lead accumulation following exposure
- Moderately reduced risk of prostate cancer

Clinical Management Considerations

- Carriers of the (+) allele benefit from vitamin D supplementation™ in comparison to (–)
- Ensure adequate calcium intake
- Vitamin K may help to compensate for the higher risk of bone loss
- Caffeine intake >300 mg/day may accelerate bone loss, especially with lower calcium intake
- Favorable bone response to alendronate and raloxifene and HT

GENOVA DIAGNOSTICS

Case #3 (Cont.)

- Decrease progesterone 175 mg E4M qhs
- Start DHEA 5 mg E4M qm
- Start testosterone 1.0 mg cream
- Start biest cream 0.75 mg cream
- Start adaptogenic herbs
- Start stress reduction techniques
- Return in 3 months for reevaluation.

Endo +

- As you have seen the new Endo+ test is a wonderful way of evaluating the patient with all the necessary information contained in one test!

Pamela W. Smith, MD, MPH, MS
faafm63.yahoo.com
personalizedmedicinecertification.com

Explore

WWW.GDX.NET

for more information and educational resources, including…

GDX Learning Library – Brief video modules and previous webinar recordings

Conferences – Schedule of events we attend

Test Menu – Detailed test profile information

MY GDX – Order materials and get results

Thank You

GENOVA DIAGNOSTICS