TEST REPORT

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ZRT LABORATORY

 # 2018 07 01 007 U

Ordering Provider:
Getuwell Clinic
Jim Getuwell, DO

Samples Received
07/31/2018

Report Date
08/05/2018

Samples Collected
Urine - 07/26/18 08:00
Urine - 07/26/18 10:00
Urine - 07/26/18 19:20
Urine - 07/26/18 22:30

Patient Name: Advanced Metabolites
Patient Phone Number: 555 555 5555

Gender	Last Menses	Height	Waist
Female	Unspecified	5 ft 3 in	Unspecified
DOB	**Menses Status**	**Weight**	**BMI**
3/4/1960 (58 yrs)	Postmenopausal	165 lb	29.2

TEST NAME	RESULTS | 07/26/18	RANGE
Urinary Estrogens		
Estradiol	0.68 L	0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	2.85	2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	0.83	0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	0.24 L	>0.3 (> median value)
2-OH Estradiol	0.21	0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	1.09	0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.15	0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	0.47	0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	0.31 L	0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	4.19	1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.06	0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	0.51	0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.47 H	0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	0.05 H	<0.04 µg/g Cr
4-MeO Estrone	0.12 H	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.26 H	0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.33 H	0.10-0.29 Premeno-luteal or ERT
Bisphenol A	<dl L	1.5-4.5 µg/g Cr Postmenopausal

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TEST NAME	RESULTS | 07/26/18	RANGE
Urinary Progestogens		
Pregnanediol	8071 H	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	35.33 H	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	148.31 H	14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	3.29 H	0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	15.13 H	3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	1.72	0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	1.48 L	3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	11869.12 H	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	6.44 L	8.63-37.28 µg/g Cr Postmenopausal
Androstenedione	1.95 L	2.07-7.94 µg/g Cr Postmenopausal
Androsterone	212	152-482 µg/g Cr Postmenopausal
Etiocholanolone	195 L	239-777 µg/g Cr Postmenopausal
Testosterone	0.91	0.66-2.89 µg/g Cr Postmenopausal
Epi-Testosterone	0.78	0.39-1.32 µg/g Cr Postmenopausal
T/Epi-T	1.17	0.5-3.0
5α-DHT	0.24 L	0.26-0.98 µg/g Cr Postmenopausal
5α,3α-Androstanediol	3.87	2.32-8.17 µg/g Cr Postmenopausal
Urinary Glucocorticoids		
Total Cortisol	11.88 L	13.23-39.26 µg/g Cr Postmenopausal
Total Cortisone	13.04 L	23.32-59.61 µg/g Cr Postmenopausal
Cortisol/Cortisone	0.91 H	0.5-0.7
Tetrahydrocortisol	192 L	281-711 µg/g Cr Postmenopausal
Tetrahydrocortisone	530 L	551-1474 µg/g Cr Postmenopausal
Urinary Free Diurnal Cortisol		
Free Cortisol	1.49 L	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	15.28 L	23.4-68.9 µg/g Cr (2nd Morning)

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TEST NAME	RESULTS | 07/26/18	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	2.51 L	6.0-19.2 µg/g Cr (Evening)
Free Cortisol	1.62 L	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	5.27 L	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	51.45 L	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	8.68 L	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	4.56 L	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	7.19 L	18.0 - 40.9 µg/g Cr (1st Morning)
Melatonin	3.39 L	7.3 - 31.9 µg/g Cr (2nd Morning)
Melatonin	0.85	0.7 - 2.2 µg/g Cr (Evening)
Melatonin	1.03 L	1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine		
Creatinine (pooled)	1.34	0.3-2.0 mg/mL
Creatinine	1.23	0.3-2.0 mg/mL (1st morning)
Creatinine	1.98	0.3-2.0 mg/mL (2nd morning)
Creatinine	2.49 H	0.3-2.0 mg/mL (Evening)
Creatinine	1.80	0.3-2.0 mg/mL (Night)

<dL *= Less than the detectable limit of the lab.* ***N/A*** *= Not applicable; 1 or more values used in this calculation is less than the detectable limit.* ***H*** *= High.* ***L*** *= Low.*

Therapies

0.5mg topical Divigel (Estradiol) (Pharmaceutical) (1 Days Last Used)125mg oral Progesterone (compounded) (1 Days Last Used)

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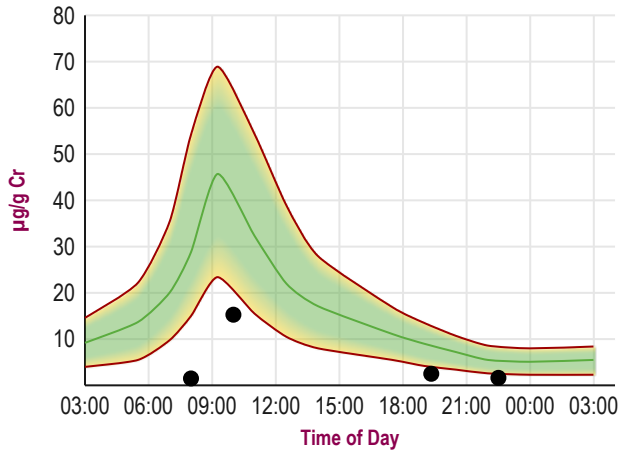
Graphs

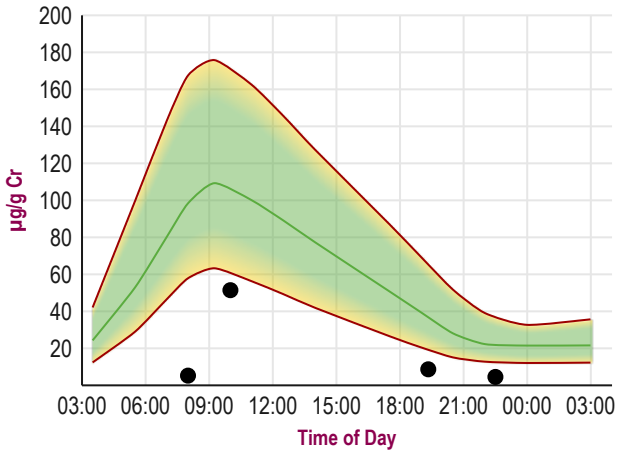
Disclaimer: Graphs below represent averages for healthy individuals not using hormones. Supplementation ranges may be higher. Please see supplementation ranges and lab comments if results are higher or lower than expected.

Average ▼▲ Off Graph

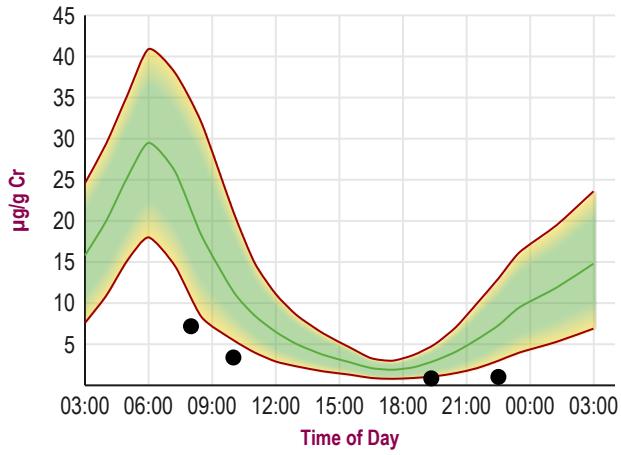
Urinary Free Cortisol



Urinary Free Cortisone



Urinary Melatonin (MT6s)



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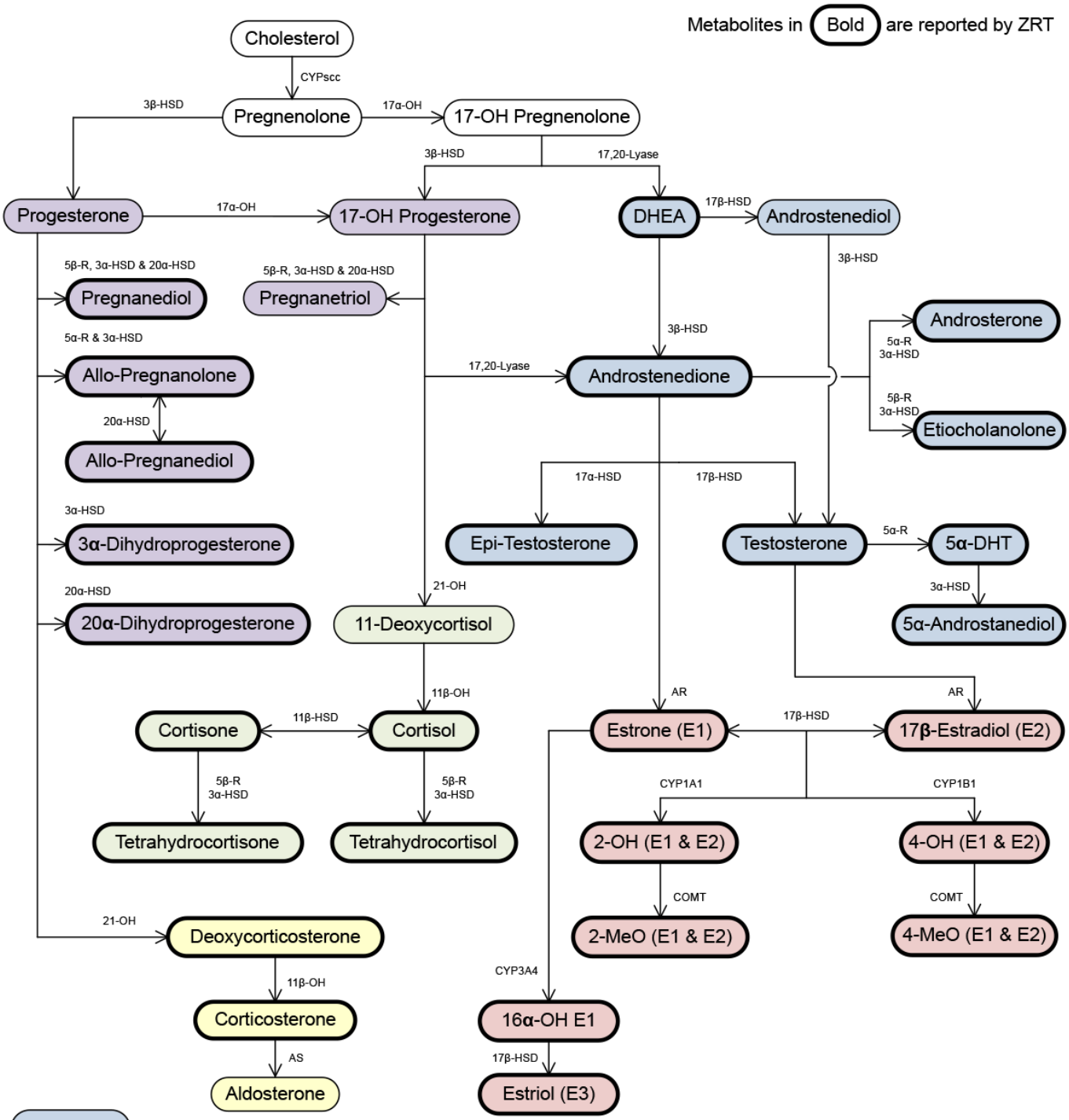
The Steroid Hormone Cascade



Enzyme Abbreviations

(5α-R) 5α-Reductase
(5β-R) 5β-Reductase
(11β-OH) 11β-Hydroxylase
(17α-OH) 17α-Hydroxylase
17,20-Lyase (same enzyme as 17α-OH)
(21-OH) 21-Hydroxylase
(3α-HSD) 3α-Hydroxysteroid dehydrogenase
(3β-HSD) 3β-Hydroxysteroid dehydrogenase
(11β-HSD) 11β-Hydroxysteroid dehydrogenase
(17α-HSD) 17α-Hydroxysteroid dehydrogenase
(17β-HSD) 17β-Hydroxysteroid dehydrogenase
(20α-HSD) 20α-Hydroxysteroid dehydrogenase
(AR) Aromatase
(AS) Aldosterone Synthase
(CYP) Cytochrome p450 (scc, 1A1, 1B1 & 3A4)
(COMT) Catechol-O-Methyl-Transferase

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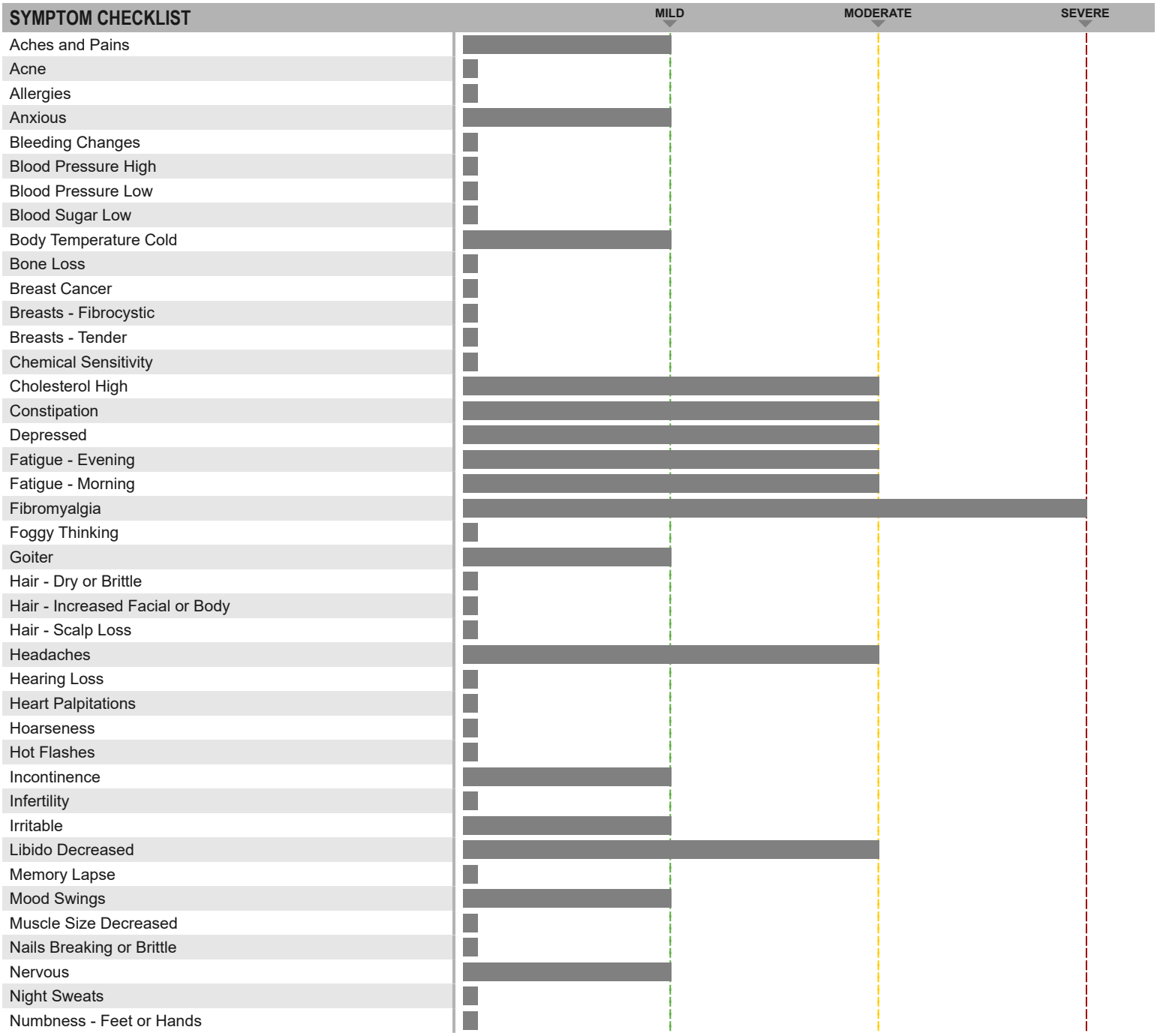
Disclaimer: Symptom Categories below show percent of symptoms self-reported by the patient compared to total available symptoms for each category. For detailed information on category breakdowns, go to www.zrtlab.com/patient-symptoms.

SYMPTOM CATEGORIES	RESULTS | 07/26/18
Estrogen / Progesterone Deficiency	18%
Estrogen Dominance / Progesterone Deficiency	20%
Low Androgens (DHEA/Testosterone)	30%
High Androgens (DHEA/Testosterone)	11%
Low Cortisol	29%
High Cortisol	28%
Hypometabolism	30%
Metabolic Syndrome	40%



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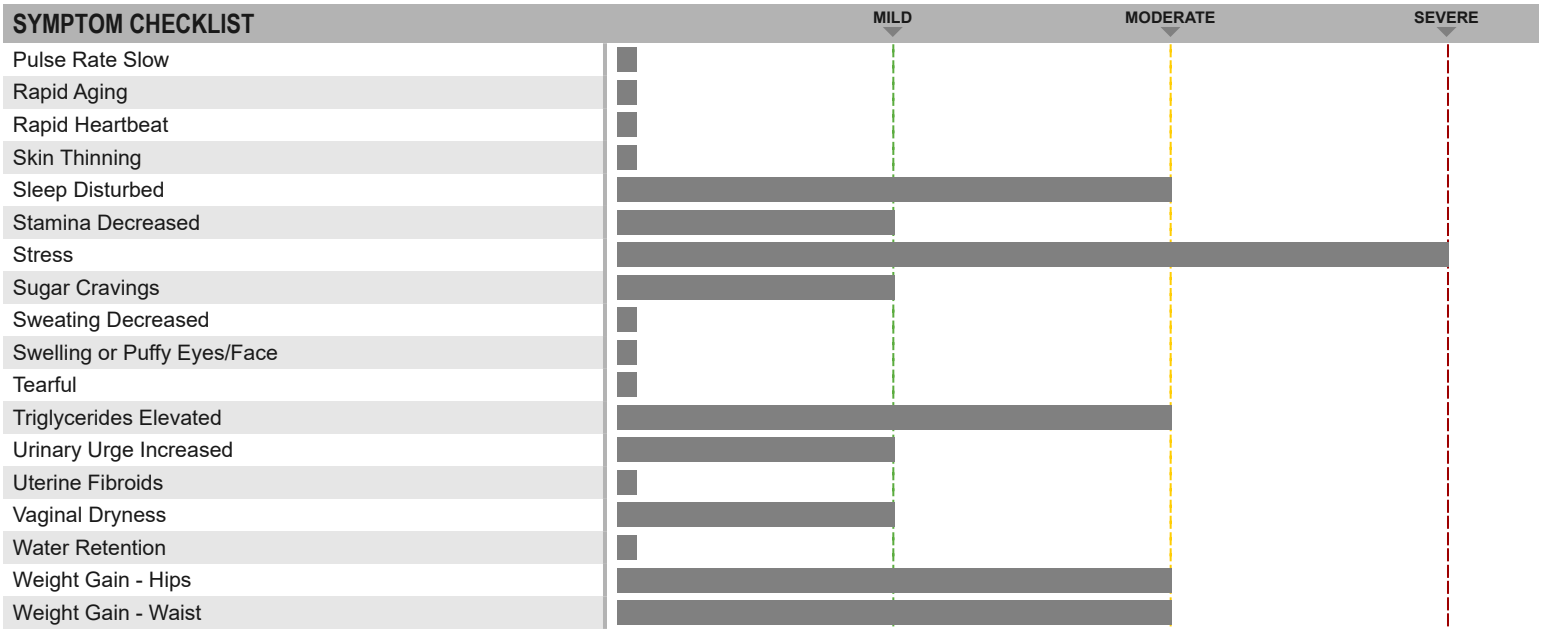

Lab Comments

PARENT ESTROGENS (ESTRADIOL-E2, ESTRONE-E1, ESTRIOL-E3)

The parent estrogens are within/near the expected median to 90 percentile of the reference ranges seen in postmenopausal women supplementing with topical estrogen replacement therapy (Note: transdermal and topical estrogens raise urinary estrogens very little as these estrogens are excreted predominately in bile and feces by this route of administration) . This is commonly seen in postmenopausal women taking low dose topical estrogens (usually a topical estradiol or biestrogen containing estradiol + estriol). Topically delivered estrogens increase saliva and capillary blood levels of the supplemented estrogens, but increase urinary and serum levels much less. Topically delivered hormones are more likely to be excreted in bile/feces than in urine.

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1, 16-OH E1) and 2-OH/16-OH RATIO

The hydroxylated estrogens are all within/near normal reference ranges for a postmenopausal woman supplementing with topical estrogen(s). Levels of the down-stream hydroxylated estrogens are usually within the low end of the reference ranges with topical ERT, as are the parent estrogens from which they are derived. Topically delivered estrogens raise the level of urinary estrogens very little, which is likely due to excrettion more in the bile/feces than in urine.

The hydroxylation of estradiol and estrone represent the first phase of metabolism and elimination of these estrogens via urine. Following hydroxylation at the 2-, 4-, or -16 position, the estrogens undergo further modification (methylation, sulfation, glucuronidation) that increases their solubility and excretion in urine. In the laboratory these sulfate and glucuronide groups are removed by enzyme hydrolysis, which allows for measurement of the different types of hydroxylated estrogens, in addition to methylation of the hydroxyl groups (see below). The 2- and 4-hydroxylated E1 and E2 metabolites are referred to as catechol estrogens.

Research and clinical studies show that the 2-hydroxylated estrogens (2-OH E2 and 2-OH E1) are a safer pathway of hydroxylation than the 4-hydroxyestrogens (4-OH E2 and 4-OH E1), which bind to and damage DNA, leading to mutations that are associated with increased breast cancer risk. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010; and Lee, JR, Zava DT What Your Doctor May Not Tell You About BREAST CANCER: How Hormone Balance Can Help Save Your Life: Chapter 7.

2-hydroxylated estrogen metabolism is increased with cruciferous vegetables and extracts of them, so higher consumption of these foods will enhance the safer 2-hydroxylation pathway for estrogen metabolism. The most commonly used concentrated extracts of cruciferous vegetables contain high levels of indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Iodine also increases the 2-hydroxylation of estrogens, with a slight increase in 4-hydroxylation (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008), which is associated with the protective effects of higher dose iodine therapy for prevention of breast cancer. The more dangerous 4-hydroxylated estrogen metabolism is enhanced by exposure to environmental toxins, mostly petrochemical-based products but also heavy metals, that induce 4-hydroxylation pathway enzymes (1B1), and cause formation of Reactive Oxygen Species (ROS) that co-oxidize the catechol estrogens to quinones.

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). Early clinical research in humans suggested that a high urinary level of 16-hydroxyestrone relative to 2-hydroxylated estrogens (i.e. a low 2-OH E1 + 2-OH E2/16-OH E1 ratio), was associated with an increased risk of breast cancer in premenopausal women, but not in postmenopausal women. This has remained controversial and newer research suggests that while higher levels of 16-hydroxy estrone may indeed be slightly associated with

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increased breast cancer risk in premenopausal women, higher levels are, paradoxically, associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). Overall, more recent studies have not shown the 2/16 ratio to be useful for predicting breast cancer risk.

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2- and -4-hydroxyestrogens are within mid range with the exception of 4-MeO-E1, which is high. This is likely a result of estrogen replacement therapy in combination with natural progesterone therapy. Progesterone induces synthesis/activation of 17 beta hydroxysteroid dehydrogenase type II, which converts estradiol to estrone (see Steroid Metabolism Cascade). Estrone is then methylated to 4-MeO-E1. Mid-range to elevated levels of methoxy-estrogens, particularly the 4-MeO-E1 and -E2 is beneficial as this indicates the potentially dangerous hydroxylated estrogen metabolites are rendered inert, and less likely converted to more dangerous estrogen quinones that increase risk for breast cancer.

The 2- and 4- hydroxyl estrogens are methylated by the enzyme Catechol-o-Methyl Transferase (COMT), which renders these catechol estrogens inert and harmless (Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010). In this form the methylated catechol estrogens are rapidly excreted in urine. If methylation pathways are inadequate due to low levels of COMT or lack of precursors of methylation (i.e. vitamins B6, B12, folate, betaine) the 2- and 4-hydroxyl estrogens can take a more insidious and dangerous pathway of metabolism, which is oxidation to highly reactive estrogen quinones. Estrogen quinones, especially the 4-quinone of estradiol and estrone are highly electrophilic and bind to DNA forming adducts that lead to permanent mutations in the DNA. Many studies have shown that high urinary levels of these 4-quinones of quinones of estradiol and estrone are associated with increased breast cancer risk if they are not inactivated by methylation or by glutathione sulfation. The 2- and 4-hydroxy estrogens are converted to their more dangerous oxidized quinone forms under oxidizing conditions in the cell, and this occurs rapidly in the presence of oxidized lipids, especially those from trans-hydrogenated fats. These estrogen quinones, like all oxidized and electron-hungry molecules in the body are inactivated when bound to glutathione, the most ubiquitous antioxidant in the body. However, if glutathione is low, due to insufficient levels of minerals (selenium, iodine) and vitamins (C and E), the quinone estrogens are less likely to be detoxified (inactivated) and have potential to damage cells/DNA in close proximity to their formation (i.e. the breast cell/DNA). Neither the quinone estrogens nor their interaction with DNA is measured-only the precursor hydroxyl-estrogens and their methylated metabolites.

The type of hydroxyl-estrogen formed, 2- or 4-estradiol or -estrone, and their degree of methylation is associated with breast cancer risk. Higher methylation of these estrogens, and consequent higher ratios of 4-MeO-E1/4-OH-E1 and/or 4-MeO-E2/4-OH-E2 theoretically should be associated with a lower breast cancer risk. Note that the 4-MeO-E1/4-OH E1 ratio is high (beneficial and indicates optimal methylation).

RATIO OF 4-METHYLATED HYDROXYESTROGENS/4-HYDROXYESTROGENS

The 4-hydroxylated estrogens (4-OH-E2 and 4-OH-E1) are well methylated based on the high 4-MeO-E2/4-OH-E2 and 4-MeO-E1/4-OH-E1 ratios. The ratios of the 4-hydroxyestrogens to their 4-methylated counterparts is evaluated to determine if they being adequately methylated, which renders them biochemically inert and reduces their risk for breast cancer. A good methylation index is associated with the ratio value towards the upper end, or higher, of the reference range. This is particularly true for the 4-hydroxylated estrogens, which if not methylated properly are associated with increased risk for conversion to more dangerous 4-estrogen quinones (not measured) that damage DNA causing mutations and potentially cancer. Even if higher levels of 4-hydroxylated estrone or estradiol are present, adequate methylation (higher ratio) render them potentially less harmful.

BISPHENOL A (BPA)

Bisphenol A (BPA) is within reference range. BPA is an endocrine disrupting chemical (EDC) derived from plastics used for making bottles, wraps for foods, and linings for food cans. BPA is not retained in the body for a prolonged period of time and is rapidly excreted into urine. High urinary levels of BPA indicate recent exposure to plastics that released excessive amounts of BPA into food or beverages consumed in the past 24-48 hr.

BPA acts as an EDC by binding to a activating both membrane and nuclear estrogen receptors in a manner similar to estradiol. Thus by mimicking the actions of endogenous estrogens, high levels of BPA can contribute to symptoms of estrogen dominance. High BPA levels have been associated with increased risks for many different health issues, including diabetes, breast cancer, and prostate cancer. When BPA levels are elevated, identification of its source and reducing exposure is worth considering.

PROGESTERONE METABOLITES (PREGNANEDIOL, ALLOPREGNANOLONE)

The urinary levels of the progesterone metabolites pregnanediol and allopregnanolone, a neuroactive steroid, are higher than luteal reference ranges (465-1609 ug/g Cr with oral progesterone therapy. Pregnanediol is within/near the expected reference range for oral progesterone therapy (1965-7373 ug/g Cr with 100-200 mg oral progesterone at 12-24 hr post therapy). Higher urinary levels of progesterone metabolites are common with use of oral progesterone, especially elevated pregnanediol (PgDiol). PgDiol serves as a good surrogate marker metabolite of the progesterone as levels increase in parallel with endogenous progesterone production by the ovaries.

However, with exogenous oral progesterone supplementation much of the progesterone is metabolized to pregnanediol and other metabolites (allopregnanolone) in the gut lining and liver before entering the systemic circulation. Approximately 90-95% of progesterone taken orally is converted rapidly to metabolites and excreted into urine mostly as glucuronide conjugates. Only about 5-10% of orally delivered progesterone enters the systemic circulation. Pregnane-metabolites formed from oral progesterone supplementation are usually high, as seen in these test

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results. One of these, allopregnanolone, is bioactive and freely enters the brain from the blood, where it binds to GABA receptors and induces a calming effect (anxiolytic). This contributes to oral progesterone's calming and sleep-inducing effects.

Oral progesterone at 100-300 mg oral dosing has been shown by numerous studies to be safe as regards risks for cardiovascular disease, uterine and breast cancers. However, some women poorly tolerate oral progesterone as the metabolites that form from it may cause excessive sleepiness, water retention, swollen and sore breasts, and headaches. This is likely due to excessive conversion of progesterone to allopregnanolone and/or deoxycorticosterone (DOC)-a mineralocorticoid (see DOC results).

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

The androgen precursors, androstenedione and DHEA, are lower than normal reference ranges for a postmenopausal woman.

In premenopausal women about half of the androstenedione is derived from the ovaries and the other half from the adrenals. At menopause, most of the androstenedione derives from DHEA(S) produced by the adrenal glands. DHEA is synthesized in the adrenal glands and is rapidly sulfated to DHEA-sulfate (DHEAS) to extend its half-life in blood. Androstenedione, the down-stream metabolite of DHEA, is further converted into testosterone and Epi-testosterone in near equal amounts in most individuals, or into estrone. More conversion to the estrogen, estrone, occurs in individuals with higher amounts of adipose (fat) tissue.

Low levels of these androgen precursors are associated with self-reported symptoms of low androgens. DHEA is commonly used as a supplement to raise testosterone levels in women. If low androgen symptoms persist, consider supplemental DHEA to raise testosterone levels, particularly if testosterone, or its down-stream and more potent metabolite DHT, are within mid range or lower for a postmenopausal woman.

ANDROGENS AND METABOLITES

Testosterone (T) is within reference range for a postmenopausal woman, but its more potent metabolite, 5 alpha dihydrotestosterone (DHT) is low. DHT is the most potent of the androgens and responsible for binding and activation of intracellular androgen receptors. Low DHT is consistent with self-reported symptoms of androgen deficiency.

Low androgens, particularly low DHT, is associated with many different adverse conditions (bone loss, thinning skin, vaginal dryness, incontinence, cardiovascular disease, insulin resistance/metabolic syndrome, breast cancer) and symptoms (fatigue, low stamina, depression, memory lapses, loss of sex drive, hot flashes, allergies).

Androgens are important for strengthening structural tissues such as muscles, bone, connective tissue, and skin. They also play an important role in the brain to increase the level of neurotransmitters such as dopamine, which are important for mood elevation and sex drive. Androgens are also precursors to the estrogens, estradiol and estrone. The most potent of the androgens is dihydrotestosterone (DHT), which is created from testosterone via 5a reductase. Testosterone itself is derived mostly from androstenedione and DHEA. In premenopausal women about half of the testosterone is derived from androstenedione produced by the ovaries, and the other half from peripheral conversion of DHEA manufactured in the adrenals. Following menopause the ovarian contribution of androgens is lower.
Low T likely contributes to the self-reported symptoms of androgen deficiency. Consider supplementing with DHEA or testosterone.

EPI-TESTOSTERONE AND RELATIONSHIP TO TESTOSTERONE.

Epi-testosterone (Epi-T) and testosterone (T) are created in about equal amounts from androstenedione and DHEA. The ratio of T/Epi-T should be about 1 under normal circumstances. When testosterone is supplemented with any delivery system except topical, the T/Epi-T ratio increases, which reflects an increase in the exogenous testosterone, but not Epi-T, which represents endogenous production.

TOTAL GLUCOCORTICOIDS

Total cortisol (F) and cortisone (E), and their down-stream metabolites, tetrahydrocortisol (THF) and tetrahydrocortisone (THE), are lower than the expected reference ranges. The total levels of these glucocorticoids are determined from the average of four urine collections throughout the day and are very similar to 24 hour urine values.

Low cortisol suggests adrenal exhaustion/low adrenal reserve, which is usually caused by some form of stressor such as emotional/psychological stress, sleep deprivation, low protein diet, nutrient deficiencies (particularly low vitamins C and B5), physical insults (surgery, injury, diseases, inflammatory conditions), chemical exposure, low cortisol precursors (pregnenolone, progesterone) and pathogenic infections (bacterial, viral, fungal). In a healthy individual the adrenal glands initially respond to stressors by increasing cortisol output. However, if the stressor persists the adrenal glands either continue to meet the demands of the stressor with high cortisol output, or become exhausted, wherein cortisol levels fall below normal, as in these test results.

Symptoms commonly associated with chronic low cortisol include fatigue, allergies (immune dysfunction), chemical sensitivity, cold body temp, and sugar craving. Low cortisol is often associated with symptoms of thyroid deficiency as normal physiological levels of cortisol are essential for optimal thyroid function. Adequate sleep and rest, gentle exercise, proper diet (adequate protein), natural progesterone, adrenal extracts, herbs, and nutritional supplements (vitamins C and B5) are some of the natural ways to help support adrenal function. Caution: Thyroid or androgen therapies may further lower cortisol levels and exacerbate symptoms of cortisol deficiency. These therapies are not likely to be successful if low cortisol is not first corrected by lifestyle interventions or medications.

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For additional information about strategies for supporting adrenal gland function and reducing stressors that deplete cortisol, the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "Awakening Athena" by Kenna Stephenson, MD.

URINARY FREE CORTISOL (F) AND CORTISONE (E)

Urinary free cortisol (F) and cortisone (E) are somewhat following a normal circadian rhythm but are lower than reference ranges throughout the day. Hypocortisolism is usually precipitated by some type of chronic stressor followed by adrenal exhaustion, but can also be the result of synthetic glucocorticoid use (none indicated), which suppresses endogenous cortisol synthesis by the adrenal glands.

Hypocortisolism (often referred to as adrenal exhaustion or adrenal fatigue) is most commonly caused by stressors which include: psychological stress (emotional), sleep deprivation, poor diet (low protein-particularly problematic in vegetarians), nutrient deficiencies (particularly low vitamins C and B5), physical insults (surgery, injury), diseases (cancer, diabetes), chemical exposure (environmental pollutants, excessive medications), low levels of cortisol precursors (pregnenolone and progesterone) and pathogenic infections (bacteria, viruses and fungi). A normal daily output of cortisol is essential to maintain normal metabolic activity, help regulate steady state glucose levels (important for brain function and energy production), and optimize immune function. Depletion of adrenal cortisol synthesis by a chronic stressor, sleep deprivation, and/or nutrient deficiencies (particularly vitamins C and B5) often leads to symptoms such as fatigue, allergies (immune dysfunction), chemical sensitivity, cold body temp, and sugar craving. If stressors persist, this can result in adrenal fatigue and the inability to continue cortisol production to meet the demands of the stressor. Adrenal support and reducing stressor(s) as much as possible should be considered to avoid adrenal exhaustion or the adverse effects associated with chronic low cortisol.

For additional information about strategies for supporting adrenal health and reducing stress(ors), the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "The Role of Stress and the HPA Axis in Chronic Disease Management" by Thomas Guilliams, PhD.

MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The urine melatonin metabolite MT6s is low throughout the day and not showing a normal circadian rhythm (flat pattern). This individual has self-reported issues with sleep disturbances, which may be related to low melatonin production as well as other hormonal imbalances (e.g. low or high levels of estrogens, progesterone, androgens, cortisol, thyroid hormones). Consider melatonin supplementation if no contraindications (see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html).

MT6s, a metabolite of melatonin found in urine, is used as a surrogate marker to follow the circadian rhythm of melatonin at different time points during the day. MT6s in the first morning urine is representative of the average night time melatonin production, when its synthesis by the pineal gland and presence in the bloodstream is highest (note: MT6s levels in urine lag behind blood and salivary levels about 2-3 hr, which makes early morning first void MT6s ideal for measuring melatonin levels when it is peaking about 2-3 am). The second urine void, about 2 hr later, should show MT6s dropping rapidly from the early morning value. The third urine void in the late afternoon, which represents the greatest amount of light exposure, should represent the lowest MT6s level. The last collection, just before bed, should show the MT6s rising from the afternoon nadir.

In a healthy individual, the circadian rhythm of melatonin is inversely related to cortisol, i.e. melatonin levels in blood, urine, and saliva rise with darkness and peak about 2-3 am, while cortisol falls to a nadir at this time of day. With morning and onset of light exposure, melatonin drops rapidly and cortisol begins to rise, peaking about 30 min to 1 hr after waking and exposure to light. By mid-afternoon melatonin reaches a nadir and then gradually begins to rise again with nightfall and less light exposure. Cortisol continues to fall as melatonin rises again, when both hormones reach their nadir and peak, respectively, about 2-3 am. These circadian patterns of melatonin are easily tracked with time collections of urine and measurement of MT6s.

Melatonin produced by the pineal gland in the brain and released into the circulation rapidly enters tissues throughout the body where it carries out its restorative properties. Melatonin synthesis decreases with aging and calcification of the pineal gland can result in very low production of melatonin.

Melatonin is known to have many different beneficial effects in the body. It helps slow the aging process, is a potent anti-oxidant, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone and decreases estrogens). Low melatonin caused by pineal calcification has been associated with many different dysfunctions and diseases such as immune dysfunction, neurodegenerative disorders (Alzheimer's disease, senile dementia), pain disorders, cardiovascular disease, cancers of the breast and prostate, and type 2 diabetes (Hardeland R. Aging and Disease 3 (2): 194-225, 2012). Low melatonin is also thought to contribute to a susceptibility to obesity in people with insomnia or those who do night shift work.

Low night time melatonin levels are seen in breast and prostate cancer patients. The WHO's International Agency for Research on Cancer has concluded that "shift work that involves circadian disruption is probably carcinogenic to humans", because of the suppression of melatonin production by exposure to light during the night.

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Because of its established role in the regulation of the circadian rhythm, treatment with exogenous melatonin has been found useful in people with circadian rhythm sleep disorders, such as delayed sleep phase disorder, jet lag, shift worker disorder, and the non-24-hour sleep-wake disorder most commonly found in totally blind individuals; however, its utility for the treatment of insomnia is not established and remains controversial.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms. This will be seen as very high levels of MT6s in the first and second urine voids, and often carry-over into the evening when levels should be low. Consider dosage reduction if MT6s levels are excessive throughout the daylight hours and this is associated with persistent sleepiness during the day.

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