TEST REPORT

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ZRT LABORATORY

 # D2026 04 30 **090 U**

Ordering Provider:
Getuwell

Samples Received
04/30/2026

Report Date
05/06/2026

Samples Collected
Urine - 04/27/26 06:00
Urine - 04/27/26 08:00
Urine - 04/27/26 19:00
Urine - 04/27/26 22:00

Patient Name: GCMS Hormone Metabolites and LCMS Diurnal Hormones I
Patient Phone Number:

Gender	Last Menses	Height	Waist
Female	04/12/2026	5 ft 7 in	26 in
DOB	**Menses Status**	**Weight**	**BMI**
1/1/1999 (27 yrs)	Pre-Menopausal	130 lb	20.4

TEST NAME	RESULTS | 04/27/26	RANGE
Urinary Estrogens		
Estradiol	1.65	0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	5.00	2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	1.28	0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	0.17 L	>0.3 (> median value)
2-OH Estradiol	1.87 H	0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	3.10 H	0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.16	0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	0.39	0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	0.83	0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	5.71 H	1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.08	0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	0.61	0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.18 L	0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	0.10 H	<0.04 µg/g Cr
4-MeO Estrone	0.03	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.07	0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.61 H	0.10-0.29 Premeno-luteal or ERT
Bisphenol A	<dl L	1.11-3.74 µg/g Cr Premeno-luteal

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TEST NAME	RESULTS | 04/27/26	RANGE
Urinary Progestogens		
Pregnanediol	1229	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	20.01 H	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	90.12 H	14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	3.00 H	0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	6.19	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	8.37	3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	790.82 L	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	92.05	15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	10.19	3.93-13.53 µg/g Cr Premeno-luteal or ART
Androsterone	1437 H	248-937 µg/g Cr Premeno-luteal or ART
Etiocholanolone	1229 H	330-960 µg/g Cr Premeno-luteal or ART
Testosterone	3.19	1.22-3.97 µg/g Cr Premeno-luteal or ART
Epi-Testosterone	7.79 H	2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	0.39 L	0.5-3.0
5α-DHT	1.05	0.28-1.52 µg/g Cr Premeno-luteal or ART
5α,3α-Androstanediol	12.11	2.98-13.10 µg/g Cr Premeno-luteal or ART
Urinary Glucocorticoids		
Total Cortisol	31.99	12.26-33.12 µg/g Cr Premeno-luteal
Total Cortisone	56.20 H	23.27-50.88 µg/g Cr Premeno-luteal
Cortisol/Cortisone	0.56	0.5-0.7
Tetrahydrocortisol	261	214-546 µg/g Cr Premeno-luteal
Tetrahydrocortisone	1154	437-1184 µg/g Cr Premeno-luteal
Urinary Free Diurnal Cortisol		
Free Cortisol	10.35	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	68.01	23.4-68.9 µg/g Cr (2nd Morning)
Free Cortisol	9.47	6.0-19.2 µg/g Cr (Evening)

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TEST NAME	RESULTS | 04/27/26	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	2.69	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	41.33	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	110.91	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	68.09	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	17.28	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	37.01	18.0 - 40.9 µg/g Cr (1st Morning)
Melatonin	28.99	7.3 - 31.9 µg/g Cr (2nd Morning)
Melatonin	0.49 L	0.7 - 2.2 µg/g Cr (Evening)
Melatonin	1.79	1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine		
Creatinine (pooled)	0.93	0.3-2.0 mg/mL
Creatinine	1.34	0.3-2.0 mg/mL (1st morning)
Creatinine	1.78	0.3-2.0 mg/mL (2nd morning)
Creatinine	0.81	0.3-2.0 mg/mL (Evening)
Creatinine	1.71	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

oral Vitamin D3 (OTC) (24 Hours Last Used)

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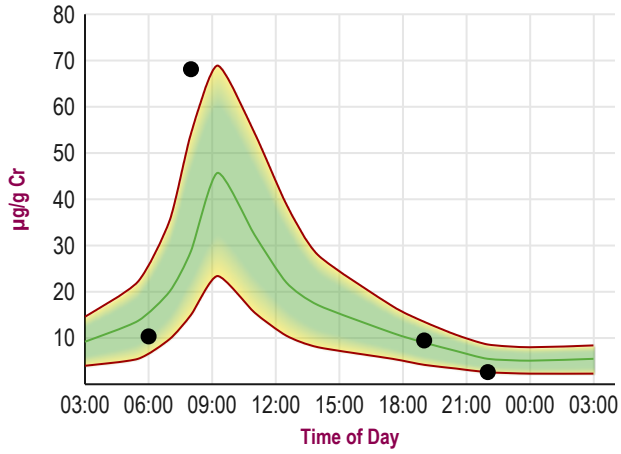
Graphs

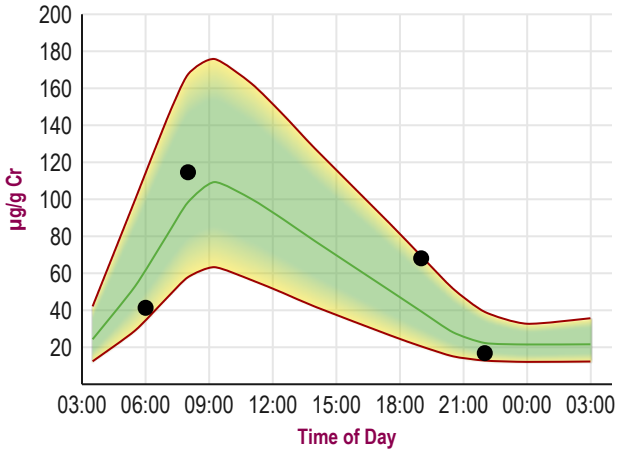
Disclaimer: Graphs below represent averages for healthy individuals not using hormones. Supplementation ranges may be higher. Please see supplementation ranges and lab comments if results are higher or lower than expected.

Average ▼▲ Off Graph

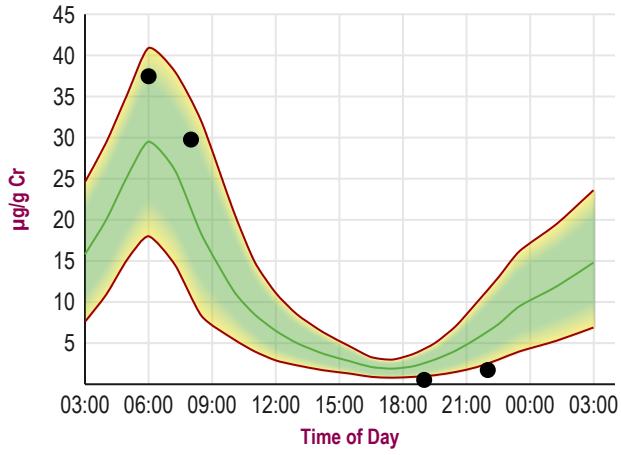
Urinary Free Cortisol



Urinary Free Cortisone



Urinary Melatonin (MT6s)



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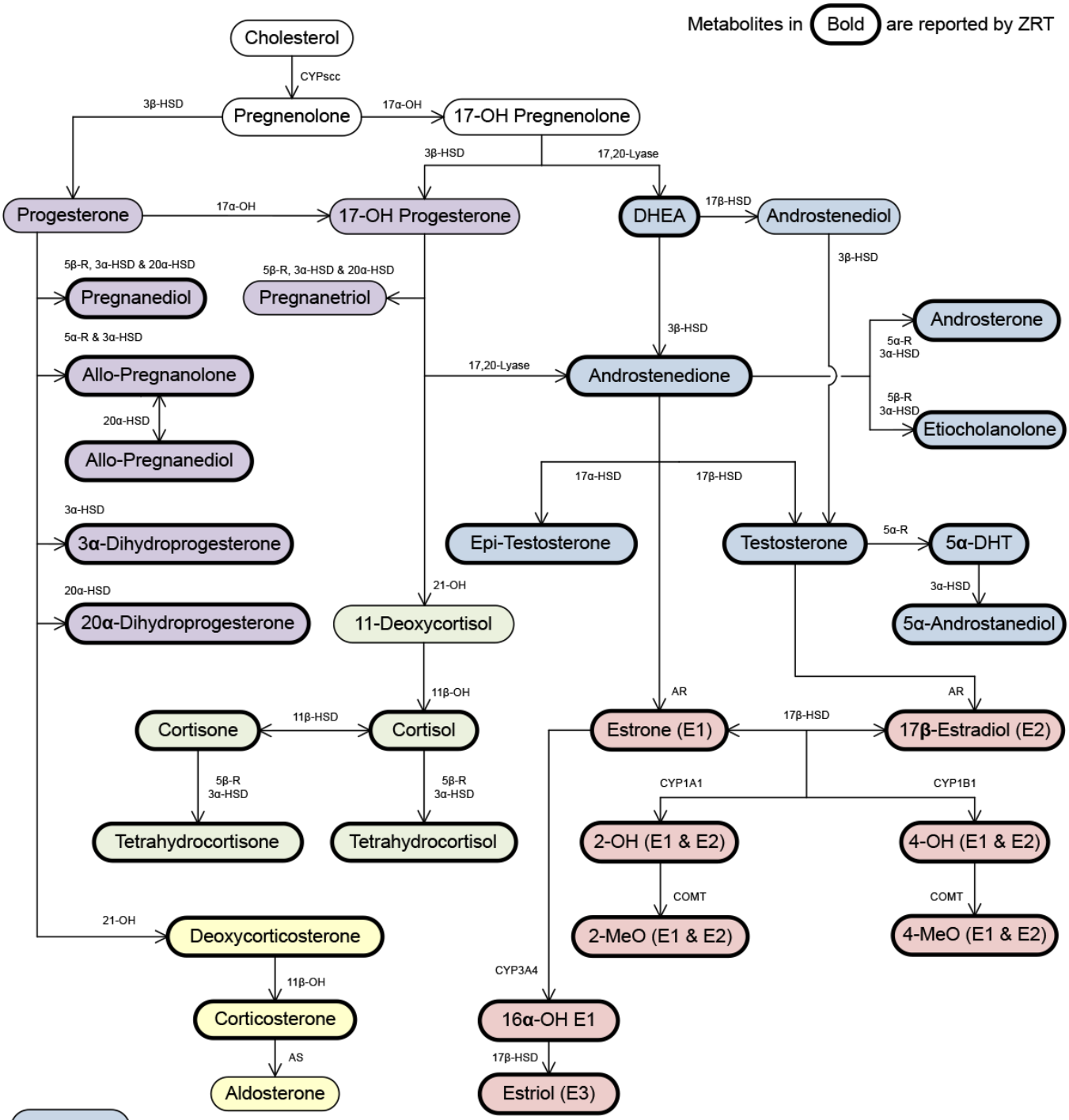
The Steroid Hormone Cascade



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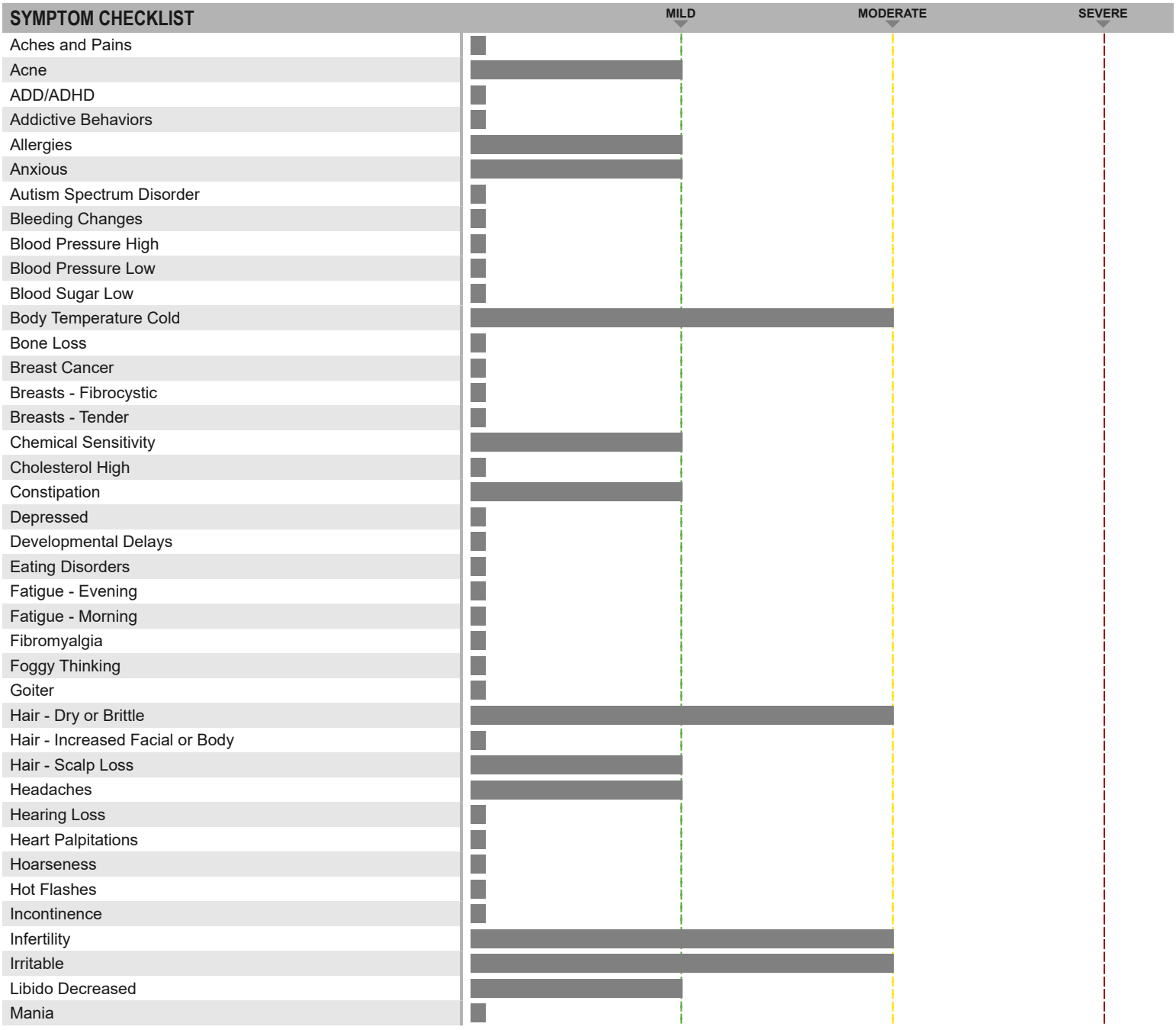
Disclaimer: Symptom Categories below show percent of symptoms self-reported by the patient compared to total available symptoms for each category. For detailed information on category breakdowns, go to www.zrtlab.com/patient-symptoms.

SYMPTOM CATEGORIES	RESULTS | 04/27/26
Estrogen / Progesterone Deficiency	6%
Estrogen Dominance / Progesterone Deficiency	15%
Low Androgens (DHEA/Testosterone)	7%
High Androgens (DHEA/Testosterone)	14%
Low Cortisol	20%
High Cortisol	13%
Hypometabolism	17%
Metabolic Syndrome	0%



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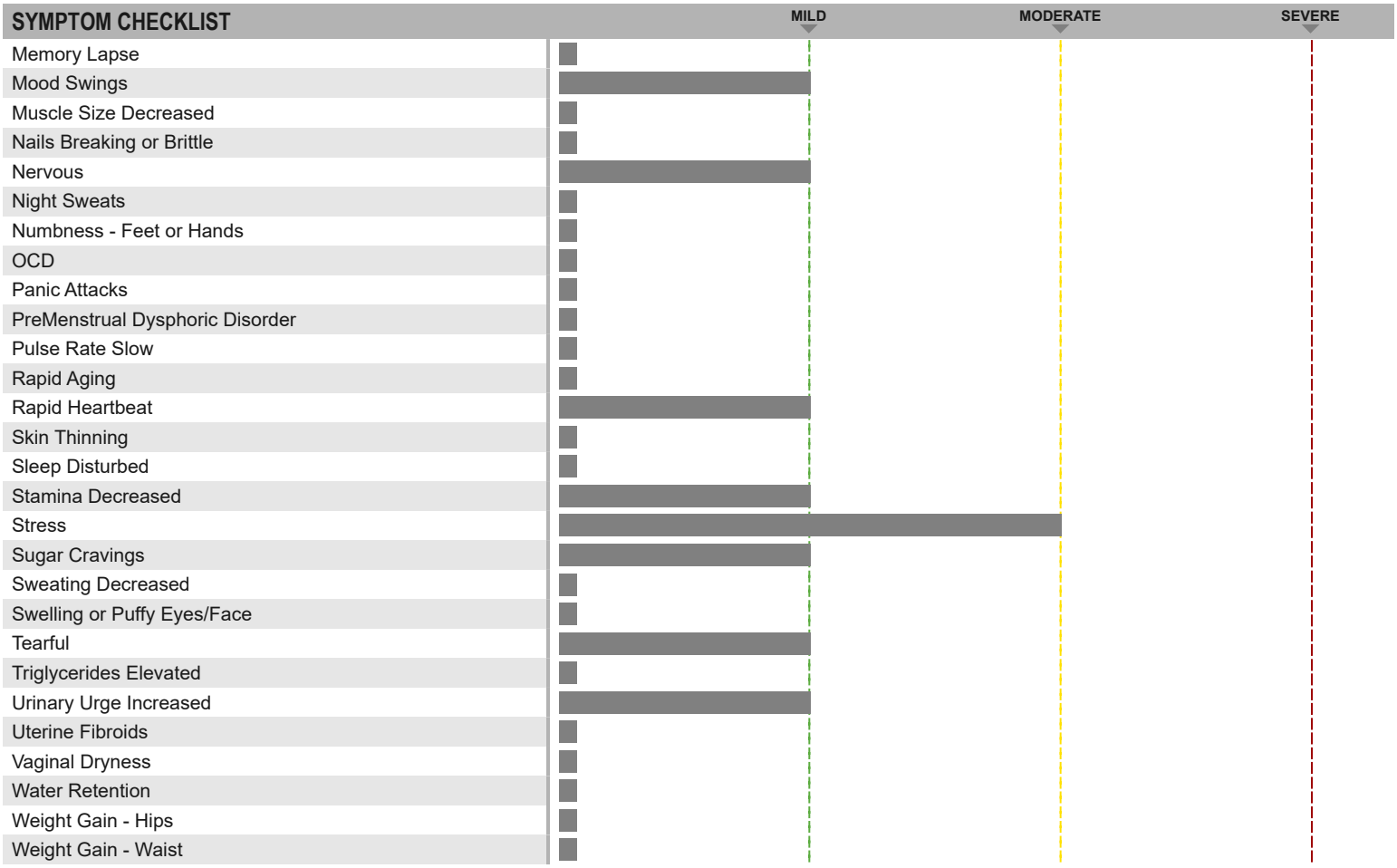

Lab Comments

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

The parent estrogens are within/near (slightly higher or lower) the expected reference ranges seen in premenopausal women.

In premenopausal women with normal ovarian estrogen synthesis It is important that estradiol, the most potent of the three estrogens, is well balanced with natural progesterone to prevent excessive proliferation of estrogen-sensitive tissues such as the uterus and breasts. This is especially important if symptoms of estrogen excess (dominance) are problematic. If the ratio of pregnanediol (progesterone surrogate marker) to estradiol is low then progesterone restoration therapy, regular exercise, eating a healthy diet with more vegetables and less red meat, and nutritional supplements such as DIM and I3C are often helpful to accelerate estrogen clearance and prevent adverse symptoms. In the premenopausal patient estradiol should be well balanced with progesterone (optimal PgDiol/E2 ratio = 1300-2000 ug/g Cr.

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1)

The 2-hydroxylated estrogens (2-OH-E2 and 2-OH-E1) are higher than reference ranges (considered beneficial); 4-OH-E2 and 4-OH-E1 are within reference range but higher than the median of the reference range. Estrone, and its hydroxylated metabolites (2-OH-E1 and 4-OH-E1) are derived from androstenedione, whereas estradiol, and its hydroxylated metabolites (2-OH-E2 and 4-OH-E2) are derived from testosterone (see Steroid Hormone Cascade).

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), the latter of which if not inactivated by methylation can be further oxidized to estrogen quinones that, if not inactivated by sulfation, bind to and damage DNA, leading to mutations that are associated with increased risk of estrogen-sensitive tissues (e.g. prostate, breasts). For this reason it is important to keep the levels of the parent estrogens (estradiol and estrone) as well as their down-stream hydroxylated forms (especially 4-OH-estrogens) within physiological levels to avoid toxic effects from them. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010.

The safer 2-hydroxylation of estradiol and estrone is increased with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Iodine also increases the 2-hydroxylation of estrogens, with a slight increase

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in 4-hydroxylation (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008). 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). When these 4-catechol estrogens react with Reactive Oxygen Species (ROS) they are co-oxidized to much more reactive quinone estrogens. The 4-quinone estrogens, if not inactivated by the sulfur groups of glutathione, can potentially bind to and damage DNA, leading to mutations that may cause cancer.

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). While higher levels of 16-hydroxy estrone may be slightly associated with increased breast cancer risk in premenopausal women, but paradoxically lower risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012), very little is known about the role of this estrogen, or its down-stream metabolite, estriol, in risk for prostate cancer.

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2-hydroxyestrogens are within or near normal reference range. The methylated forms of the 4-hydroxyestrogens, on the other hand, are within the upper quadrant of the reference ranges or higher. The ratio of 4-MeO-E2/4-OH-E2 is also high, indicating good methylation. High methylation of the catechol estrogens, particularly the more toxic and mutagenic 4-OH-E2 is considered beneficial as it prevents the 4-OH-E2 from potentially converting to more toxic and mutagenic estrogen quinones.

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. However, 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 of the hydroxyl (catechol) groups to 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 estradiol and/or 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. Increased levels of 4-hydroxy estrone or 4-hydroxy estradiol are associated with increased breast cancer risk. In contrast, formation of the 2-hydroxylated estrogens is associated with a lower breast cancer risk; however, very high levels of 2-hydroxylated estrogens, if not associated with concomitant methylation are also associated with increased risk.

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-PgDiol, Allopregnanolone-AlloP)

The progesterone metabolite pregnanediol (PgDiol) is within expected reference range for a premenopausal women. PgDiol is a metabolite and surrogate marker of serum progesterone; PgDiol in urine rises in parallel with levels of Pg in blood and saliva of premenopausal women during the luteal phase of the menstrual cycle. If the PgDiol/E2 ratio is low this usually indicates luteal insufficiency. Consider progesterone therapy if PgDiol/E2 is low, and symptoms of estrogen dominance are problematic.

In contrast to normal levels of PgDiol, the neuroactive progesterone metabolite allopregnanolone (AlloP) is higher than reference range. This suggests that the level/activity of enzyme 5-alpha reductase is high as this enzyme converts progesterone to 5-hydroxyprogesterone (5-HP) which is then converted to AlloP by the enzyme 3 alpha hydroxysteroid dehydrogenase (see Steroid Hormone Cascade). High levels of AlloP are often associated with high levels of other steroids that are metabolized by 5-alpha reductase (e.g. testosterone to dihydrotestosterone).

AlloP is a potent neuroactive steroid that freely enters the brain from the bloodstream through the blood brain barrier where it binds to GABAa receptors in neurons inducing a calming (anxiolytic) and sleep-inducing effect. Only high levels of AlloP, achieved at peak of an optimal luteal

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phase, during pregnancy, and with progesterone therapy, have the anxiolytic effects on GABAa receptors in the brain. In a small percentage (about 5-10%) of premenopausal women AlloP at physiological levels has a paradoxical effect and causes anxiety (anxiogenic) and other symptoms characteristic of premenstrual dysphoric disorder (PMDD).

PROGESTERONE METABOLITES: MINERALCORTICOID PRECURSORS

Deoxycorticosterone (DOC) and cortiscosterone (CC) are within/near the expected reference ranges for a premenopausal woman. DOC and CC are downstream metabolites of progesterone and progesterone therapy, particularly oral progesterone, usually increases DOC and CC beyond reference ranges.

DOC is a weak mineralcorticoid and precursor to the more potent mineralcorticoid aldosterone. The conversion of progesterone to DOC varies by up to 20-fold among women (MacDonald Endocrine Reviews 12: 372-401, 1991) p. 390). Adverse reactions to higher progesterone that occur during the luteal phase of the menstrual cycle, pregnancy, or with progesterone replacement therapy may involve high conversion to DOC.

ANDROGEN PRECURSOR (DHEA/S)

Total urinary DHEA(S) and its downstream hormone androstenedione are within normal reference ranges. DHEA is synthesized in the adrenal glands and is rapidly sulfated to DHEA-sulfate (DHEAS) to extend its half-life in blood. DHEA is converted to androstenedione and then to 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.

DHEA is considered a universal precursor to both androgens (androstenedione, testosterone, DHT), and estrogens (estradiol and estrone). DHEA is commonly used as a supplement to raise both DHEA and testosterone levels in women. Much less DHEA is converted to T and DHT in men.

DHEA itself has very little androgenic activity and serves mostly as a precursor to other downstream more potent metabolites (androgens and estrogens). In the sulfated form DHEA sulfate (DHEAS) plays an important role in the integrity of the immune system via binding to specific DHEAS binding sites on lymphocytes. In the brain DHEAS acts as a neuroactive steroid where it modifies dopaminergic pathways responsible for uplifting mood and increasing feeling of wellbeing.

DHEA/ANDROSTEINE METABOLITES: (ANDROSTERONE-ANDROS, ETIOCHOLANOLONE-ETIO)

Androsterone (Andros) and etiocholanolone (Etio) are higher than reference ranges. Both are downstream metabolites of androstenedione, which is a metabolite of DHEA (see Steroid Hormone Cascade). High DHEA contributes to high levels of these downstream metabolites. DHEA is converted to androstenedione via 3 beta-HSD and then into etiocholanolone by 5-beta-reductase. DHEA is metabolized to androstenedione and then to androsterone by 5-alpha-reductase (see Hormone Cascade).

High DHEA and its downstream metabolites is usually a result of oral DHEA therapy, Congenital Adrenal Hyperplasia (CAH), or more rarely an adrenal tumor.

ANDROGENS AND METABOLITES

Testosterone (T), and its more potent metabolite, 5-alpha DHT (DHT) are within the mid to high expected reference range for a premenopausal woman. Epi-testosterone (Epi-T), on the other hand, is much higher than the reference range. This is unusual since T and Epi-T are usually produced in equal amounts from androstenedione, a down-stream metabolite of DHEA.

While Epi-T and T are normally created in about equal amounts and the ratio of T/Epi-T is usually about 1 (normal range 0.5-3), T and DHT can be much lower than Epi-T, resulting in a very low T/Epi-T ratio. Low urinary T and DHT occurs more frequently in men and women of Asian and Indian (Asian Continent) descent due to deletion polymorphisms in testosterone glucuronidation. This results in less glucuronidation of testosterone and consequently less of the T-glucuronide conjugate excreted in urine, despite normal levels of T in serum (Jakobsson J J Clin Endocrinol Metab 91: 687-693, 2006; Strahm E. Br J Sports Med 43: 1126-1130, 2009). T levels in saliva and capillary blood (Dried Blood Spots-DBS) would also be within normal range despite the "apparent" low T seen in urine. When T and DHT are low and Epi-T is higher than range, especially if symptoms of high androgens are problematic, testing of blood or saliva may provide a more accurate result of the true circulating level of testosterone.

Physiological levels of androgens (T and DHT) 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. T is also a precursor to estradiol via the enzyme aromatase.

High androgens in premenopausal women often indicate Polycystic Ovarian Syndrome (PCOS), which is closely associated with obesity, insulin resistance, and metabolic syndrome. Testosterone serves as a precursor to estrogens via aromatase. If estrogens are high and symptoms problematic consider testing saliva, DBS, or serum for total testosterone.

5-ALPHA 3-ALPHA ANDROSTANEDIOL (ADIOL)

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The downstream metabolite of DHT, 5-alpha 3-alpha androstanediol (Adiol), is within expected reference range. Adiol is considered a neuroactive steroid that can passively enter the brain from the bloodstream through the blood brain barrier.

Adiol binds to GABAa receptors in the brain and has a similar anxiolytic (calming) effect, albeit weaker than allopregnanolone. It also interacts with the dopaminergic pathways in the brain and is associated with the dopamine pleasure and reward pathway. Thus, low levels of Adiol are more likely to be associated with conditions/symptoms common to low dopamine, and high levels with high dopamine. Fibromyalgia and chronic fatigue syndrome (CFS) are common in individuals with low dopamine, as are symptoms of brain fog, achy muscles, and excessive fatigue.

TOTAL GLUCOCORTICOIDS (F, E, THF, THE)

Total cortisol (F) and cortisone (E), and their down-stream metabolites, tetrahydrocortisol (THF) and tetrahydrocortisone (THE), are within/near the normal reference ranges.

The total levels of these four glucocorticoids are determined from the average of four urine collections throughout the day and are very similar to the 24-hour urine values. To appreciate baseline and supplemented cortisol levels it is more appropriate to test cortisol levels throughout the day (following cortisol therapy) by the urinary free cortisol test (see below).

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; "Awakening Athena" by Kenna Stephenson, MD.

URINARY FREE CORTISOL (F) AND FREE CORTISONE (E)

Urinary free cortisol (F) and free cortisone (E) are following a normal circadian rhythm and are within/near normal reference ranges throughout the day. This individual has self-reported minimal symptoms characteristic of hypothalamic-pituitary-adrenal dysfunction, consistent with normal cortisol and cortisone levels.

For additional information about adrenal dysfunction and associated symptoms the following books and journal articles 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 melatonin metabolite, 6-sulfatoxymelatonin (MT6s), is within or near normal reference ranges throughout the day, and showing a normal circadian rhythm.

In a healthy individual the circadian rhythm of melatonin is inversely related to cortisol. 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. While melatonin and cortisol levels are inversely related during the light-dark cycles of the day, neither directly controls the synthesis of the other. Melatonin synthesis by the pineal gland is controlled almost exclusively by light exposure, while cortisol synthesis is controlled by the hypothalamic-pituitary axis in response to stress(ors).

The circadian patterns of melatonin are easily tracked with collections of urine timed throughout the day and measurement of 6-sulfatoxymelatonin (MT6s), a stable metabolite of melatonin and surrogate marker of melatonin synthesis. MT6s levels in urine lag about 2-3 hours behind active circulating levels of melatonin found in blood and saliva, which makes early morning first void MT6s measurements convenient for determining melatonin's average synthesis during the dark-hours at night during sleep. Sleep disturbances, which may result in high cortisol during the night, do not necessarily control melatonin synthesis by the pineal gland; this is regulated by light exposure. Stress during the dark hours may result in insomnia and more light exposure, which lowers melatonin synthesis.

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, the latter of which 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, regulates the immune system, 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 excessive light exposure during the dark hours, or calcification of the pineal gland caused by aging, 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 obesity in people with insomnia or those who do night shift work (Fonken LK and Nelson RJ. Endocrine Reviews 35: 648-670, 2014).

The above results and comments are for informational purposes only and are not to be construed as medical advice. Please consult your healthcare practitioner for diagnosis and treatment.

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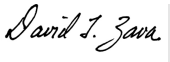
The WHO's International Agency for Research on Cancer has concluded that "shift work that involves circadian disruption is probably carcinogenic to humans", because of the suppression of melatonin production by exposure to light during the night. Low night time melatonin levels are seen commonly in breast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

Because of its established role in the regulation of the circadian rhythm, melatonin supplementation 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. 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 late afternoon when levels should be low. While MT6s is an excellent surrogate marker for endogenous melatonin production, it is not as useful as a surrogate marker of melatonin with oral supplementation. Oral melatonin supplementation results in much higher MT6s levels in urine that are NOT reflective of active circulating levels of melatonin in the bloodstream and bioavailable to tissues throughout the body. Most of the melatonin taken as a supplement is rapidly metabolized by the liver (first-pass effect) and kidney and excreted into urine as MT6s. To accurately determine circulating levels of melatonin with exogenous melatonin supplementation, it is necessary to test melatonin in blood or saliva.

For more general information about melatonin please see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html

Urinary creatinine is within normal reference ranges throughout the day, based on testing diurnal 2x, 4x, or 6x urine collections.
Creatinine values slightly lower than range usually indicate overly dilute urine from excessive water intake shortly before collection, or not spacing collection of multiple urine samples by at least 2 hr (most problematic in second morning urine collection). Creatinine slightly higher than range is usually due to inadequate hydration.
Extreme low or high values may be caused by kidney or other metabolic disorders (e.g. metabolic syndrome and diabetes).



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